Syntheses in the Isoquinoline Series. Synthesis of 2,3-Dihydro-4(1H)-isoquinolones[1]

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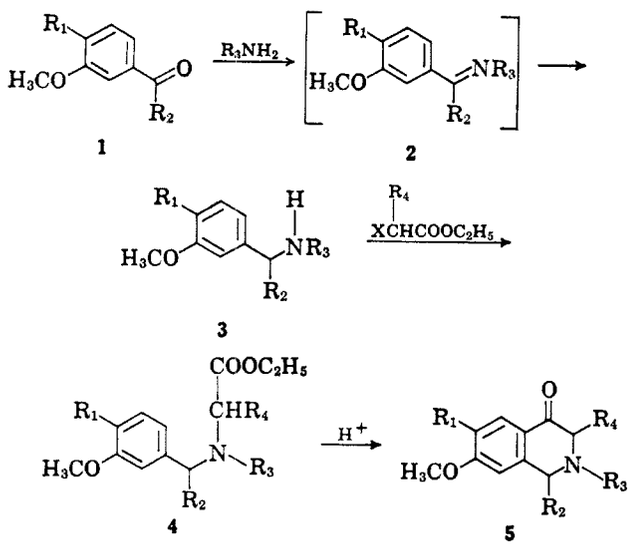
Various 2,3-dihydro-4(1H)-isoquinolones have been prepared by acid-catalyzed cyclization of N-benzylglycine derivatives.

Several authors[2] reported the preparation of 2,3-dihydro-4(1H)-quinolones in good yields by acid-catalyzed cyclization of 2-anilinopropionic acid derivatives. It occurred to us that application of this principle to the cyclization of properly substituted N-benzylglycine derivatives **4** might result in a practical method for the preparation of various 2,3-dihydro-4(1H)-isoquinolones of type **5**.[3] This approach was materialized according to Scheme I. The aldehydes

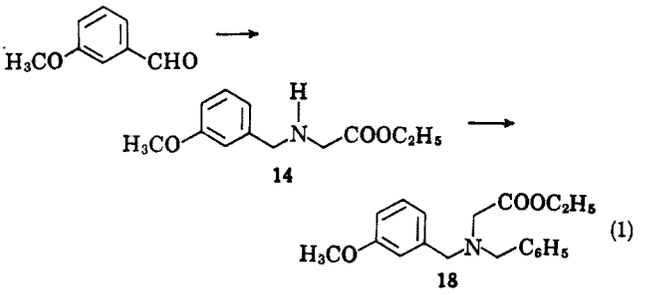
SCHEME I



(**1**, R_2 = H) or ketones (**1**, R_2 = alkyl or aryl) were condensed with the appropriate amine to yield Schiff bases **2**, which were converted readily into benzylamines **3**. Compounds **3**, on reaction with halo acetates (or by an alternate procedure), were transformed into the glycine ester derivatives **4**. Formation of the amino ketones **5** was achieved by cyclizing compounds **4** in the presence of 70–90% sulfuric acid at 100°.

Three variations for the preparation of the benzylamines **3** were studied in detail. In the first of these (method A), compound **1** (R_2 = H) was mixed with a cold solution of ammonia in methanol and then hydrogenated under pressure at elevated temperatures over Raney nickel to give primary benzylamines directly. Thus, 3-methoxybenzaldehyde gave an 80% yield of 3-methoxybenzylamine (**6**) which was contaminated with a small amount of bis-3-methoxybenzylamine. With methylamine (method B) the formation of the Schiff base **2** (R_3 = CH_3) was accomplished in ethanol under pressure at elevated temperature, whereas benzylamine condensed with **1** to give **2** (R_3 = CH_2-C_6H_5) in benzene at the reflux temperature (method C). The crude Schiff bases obtained by methods B or C were readily reduced with sodium borohydride to afford the benzylamines **3** (R_3 = methyl or benzyl) which were isolated and characterized in most cases as their crystalline hydrochlorides. The various benzylamines prepared by the above methods are described in Table I.

Reaction of the benzylamines **3** with halo acetates in benzene at the reflux temperature in the presence of sodium carbonate gave glycine ester derivatives **4** which are summarized in Table II. Some of the glycine ester derivatives **4** were obtained by a variation of the procedure as illustrated by the synthesis of compound **18** from *m*-methoxybenzaldehyde (eq 1). An ethanolic



(1)

solution of the aldehyde and glycine ethyl ester was hydrogenated over platinum oxide. The intermediate N-benzylglycine ester **14**, in ether, was converted into **18** by reaction with benzyl chloride in the presence of triethylamine.

Cyclization to the amino ketones **5** was achieved by warming the glycine esters **4** in 70–90% sulfuric acid at 100°. The yields of **5** were dependent on both the sulfuric acid concentration and the temperature. Polyphosphoric acid afforded no advantage as the cyclization agent. While the esters were usually used in the cyclization step, the acids (for example the amino acid **20**) could also be used in this reaction and under the same conditions. The 2,3-dihydro-4(1H)-isoquinolones **5** so obtained are described in Table III. This table also includes the isoquinolones prepared by hydrogenolytic debenzylation discussed below.

Most of the ring closures proceeded smoothly and in good yields. The yields were generally improved when the N-benzylglycine derivatives carried α-alkyl or aryl substituents. Substitution on the nitrogen atom was also important as illustrated by the fact that glycine derivative **14** gave only a 15% yield of the secondary amino ketone **26**. Compounds of this type (**26**, **30**, and **35**) could be obtained in good yields, however, by first preparing the N-benzyl-substituted 2,3-dihydro-4(1H)-isoquinolone hydrochlorides (**29**, **32**, and **37**), then de-

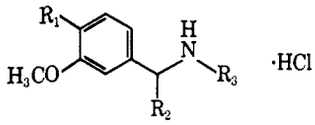
(1) In part presented by one of us (A. B.) before the Section of Chemical Science at the New York Academy of Sciences in March 1966; *Trans. N. Y. Acad. Sci.*, [II] **28**, 685 (1966).

(2) J. Koo, *J. Org. Chem.*, **28**, 1134 (1963), and references therein.

(3) During the course of our work Kametani and Fukumoto [*J. Chem. Soc.*, 4289 (1963)] reported a low yield synthesis of 2,3-dihydro-6,7-dimethoxy-1-methyl-4(1H)-isoquinolone by cyclization of N-(3,4-dimethoxy-α-methylbenzyl)glycine with polyphosphoric acid.

TABLE I

BENZYLAMINE DERIVATIVES

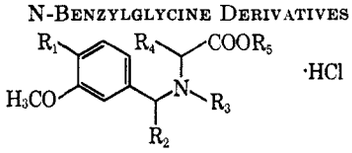


Compd	R_1	R_2	R_3	Method of preparation[a]	Yield,[b] %	Mp, °C	Crystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6	H	H	H	A	80[c]	166–167[d]	Methanol–ether	55.30	6.97	8.07	55.46	6.77	7.75
7	H	H	CH_3	B	87	124–125[e]	Isopropyl alcohol	57.59	7.52	7.46	57.91	7.53	7.40
8	H	CH_3	CH_3	B	90	153–155[f]	Acetonitrile	59.54	7.99	6.94	59.55	8.11	6.92
9	H	H	C_7H_7	C	68	128–129	Ethyl acetate	68.30	6.88	5.31	67.99	6.69	5.18
10	H	CH_3	C_7H_7	C	75	173–174	Methanol–acetone	69.18	7.26	5.05	69.51	7.51	5.01
11	H	C_6H_5	CH_3	B	97	222–223	Methanol–acetonitrile	68.38	6.87	5.32	68.54	6.59	5.33
12	OCH_3	H	CH_3	B	93	202–204[g]	Ethanol	55.17	7.41	6.44	55.18	7.21	6.44
13	OCH_3	H	C_7H_7	C	82	184–186[h]	Ethanol	65.41	6.86	4.77	65.19	6.59	4.69

[a] The different methods of preparation are described in the experimental part by typical examples. [b] Yields are based on starting aldehydes or ketones. [c] The yield was calculated for the free base which was distilled at 115–120° (10–12 mm). [d] T. Curtius [*J. Prakt. Chem.*, [2] **85**, 436 (1912)] reported mp 160°. [e] R. Baltzly and J. S. Buck [*J. Am. Chem. Soc.*, **65**, 1984 (1943)] reported mp 128.5–129°. [f] M. Macdonald and E. Stedman [*J. Chem. Soc.*, 2513 (1932)] reported mp 152–153°. [g] The free base is described by M. Tiffeneau [*Bull. Soc. Chim. France*, **9**, 930 (1911)], bp 135–140° (12 mm). [h] M. J. Adorni and M. N. Ishii [*Anales Asoc. Quim. Arg.*, **33**, 71 (1945)] reported mp 186°. The free base had bp 155° (0.1 mm).

TABLE II

N-BENZYLGLYCINE DERIVATIVES



Compd	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp or bp, °C (mm)	Crystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
14	H	H	H	H	C_2H_5	57	145–146	Acetone	55.49	6.98	5.39	55.88	6.97	5.39
15[a]	H	H	H	H	H	75	211–212	Ethanol	51.84	6.09	6.05	51.50	5.90	5.93
16	H	H	CH_3	H	C_2H_5	97	94–96	Acetone	57.03	7.36	5.12	57.24	7.36	4.93
17	H	H	CH_3	CH_3	C_2H_5	57	106–107	Benzene–ether	58.43	7.71	4.87	58.79	7.52	4.69
18[b–d]	H	H	C_7H_7	H	C_2H_5	79	153–156 (0.1)		72.82	7.40		72.62	7.21	
19	H	CH_3	CH_3	H	C_2H_5	92	133–134	Benzene	58.43	7.71	4.87	58.19	7.52	4.49
20[a]	H	CH_3	CH_3	H	H	89	152–154	Methanol–benzene	55.48	6.98	5.39	55.19	7.05	5.24
21[b]	H	CH_3	C_7H_7	H	C_2H_5	52	130–135 (0.05)		73.36	7.69	4.28	73.64	7.61	4.10
22[b]	H	CH_3	CH_3	CH_3	C_2H_5	66	120–122 (0.3)		67.89	8.73	5.28	67.73	8.65	5.13
23	H	C_6H_5	CH_3	H	C_2H_5	90	155–156	Isopropyl alcohol	65.22	6.91	4.05	65.08	7.16	3.91
24[e]	OCH_3	H	CH_3	H	C_2H_5	92	107–109	Ethanol	55.35	7.31	4.61	55.24	7.34	4.56
25[b,f]	OCH_3	H	C_7H_7	H	C_2H_5	82	172 (0.08)		69.95	7.34	4.08	70.21	7.51	3.88

[a] Prepared from compound **14** and **19**, respectively. [b] Compounds **18**, **21**, **22**, and **25** were characterized as free bases. [c] Crystalline hydrochloride of **18** (mp 114–117°) was recrystallized from acetone–ether. [d] Compound **18** was also prepared from **14**. [e] The free base of **24** was distilled at 135–136° (0.25 mm). [f] Crystalline hydrochloride of **25** (mp 140–141°) was recrystallized from acetone–ether.

benzylating them by catalytic hydrogenation. Hydrogenation of the free bases of **29** and **32** gave the isoquinolinols **38** and **39**, respectively (Scheme II).

Experimental Section[4]

Preparation of Benzylamines 3. General Procedures. Method A.—The aldehyde or ketone (1 mole) was dissolved in 900 ml of ice-cold 20% methanolic ammonia, and this solution was hydrogenated at 80–90° and 60 atm over Raney nickel. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure. Vacuum distillation of the residue gave the benzylamine in 70–80% yield. The compounds were characterized as their hydrochlorides.

Method B.—To a solution of 16 g of methylamine in 150 ml of ethanol was added 0.2 mole of the aldehyde or ketone. The mixture was heated at 70–100° under 3 atm of hydrogen pressure for 3–6 hr and, after cooling to room temperature, 0.2 mole of sodium borohydride was added to the stirred solution in small portions. After the addition was completed stirring was continued for 5 hr. The solvent was distilled under reduced pressure and *ca.* 100 ml of water was added to the residue. After warming this mixture for a short time the undissolved oil was extracted repeatedly with ether. The combined ether solutions were dried and filtered. Addition of excess isopropyl alcoholic hydrogen chloride to the ethereal filtrate gave the crystalline hydrochloride of the benzylamine in 90% yield.

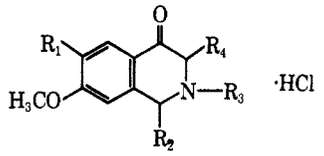
Method C.—A solution of 0.2 mole of aldehyde or ketone and 0.2 mole of benzylamine in 75 ml of benzene was refluxed until no more water was collected in a Dean–Stark water trap. The benzene was removed under reduced pressure, the residue was dissolved in 150 ml of ethanol, and 0.2 g of sodium borohydride was added to the stirred mixture in small portions. After addition was completed, stirring was continued for 2 hr. The solvent was removed under vacuum and 50 ml of water was added to the residue. After the mixture was warmed slightly for a short time, the insoluble oil was extracted repeatedly with ether. The combined ether solutions were dried and filtered. Addition of excess isopropyl alcoholic hydrogen chloride to the filtrate produced the crystalline hydrochloride of the dibenzylamine in 65–80% yield.

Preparation of N-Benzylglycine Derivatives 4. General Method.—A mixture of 0.1 mole of benzylamine **3**, 0.105 mole of ethyl halo acetate (preferably the chloro derivative), 0.15 mole of anhydrous sodium carbonate, and 100 ml of benzene

(4) Melting points were taken in capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Boiling points are not corrected. Infrared spectra were determined with a Beckman infrared spectrophotometer Model IR-5 or IR-9. The uv spectra were recorded on a Cary spectrophotometer Model 14, using isopropyl alcohol as solvent unless otherwise indicated. Organic solutions were dried over sodium sulfate.

TABLE III

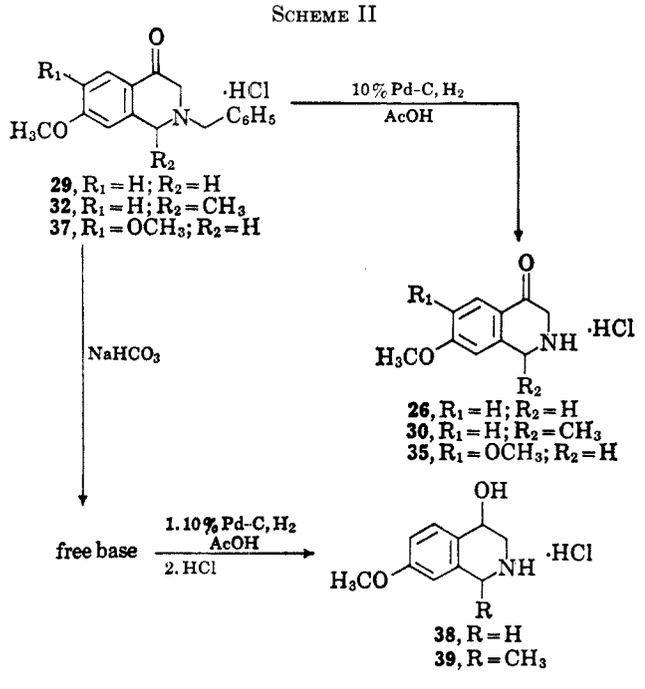
2,3-DIHYDRO-4(1H)-ISOQUINOLONES



Compd	R_1	R_2	R_3	R_4	Yield, %	Method of preparation[a]	Mp, °C	Crystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
26	H	H	H	H	15–81	A, B	A, 214–216 B, 224–225	Methanol–ether	56.21	5.66	6.56	56.02	5.50	6.56
27	H	H	CH_3	H	36	A	242–243	Methanol	58.02	6.19	6.15	58.29	6.06	6.15
28	H	H	CH_3	CH_3	40	A	195–197	Isopropyl alcohol	59.62	6.67	5.80	59.35	6.58	5.59
29[b]	H	H	C_7H_7	H	50	A	144–146	Benzene–petr ether	76.38	6.41	5.24	76.75	6.55	5.34
30	H	CH_3	H	H	78	B	213–214	Ethanol	58.02	6.20	6.15	58.16	6.47	6.27
31	H	CH_3	CH_3	H	54	A	236–237	Methanol–isopropyl alcohol	59.62	6.67	5.79	59.90	6.36	5.84
32	H	CH_3	C_7H_7	H	66	A	196–197	Ethanol	68.02	6.34	4.40	68.03	6.42	4.25
33	H	CH_3	CH_3	CH_3	49	A	217–218	Ethanol–isopropyl alcohol	61.01	7.09	5.44	61.08	7.23	5.39
34	H	C_6H_5	CH_3	H	40	A	206–207	Methanol	67.21	5.97	4.61	67.11	6.21	4.50
35	OCH_3	H	H	H	94	B	237–238	Methanol	54.21	5.79	5.75	54.29	5.95	5.65
36	OCH_3	H	CH_3	H	12	A	252–253	Methanol	55.92	6.24	5.44	55.71	6.02	5.58
37	OCH_3	H	C_7H_7	H	10	A	216–217	Methanol	64.78	6.03	4.19	64.47	6.02	4.27

[a] Method A refers to the preparation by cyclization of substituted N-benzylglycines in sulfuric acid (Scheme I), a general procedure for which is given in the Experimental Section. Method B refers to hydrogenolytic debenzylation of the corresponding N-benzyl derivative. [b] Characterized as the free base. The hydrochloride had mp 213–215° after recrystallization from methanol.

SCHEME II



was stirred and refluxed overnight. After cooling and removal of the salts by filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was covered with ether and was allowed to stand for 1 hr at room temperature. A small quantity of undissolved material was removed by filtration and discarded. The N-benzylglycines were isolated either as their crystalline hydrochlorides by addition of excess isopropyl alcoholic hydrogen chloride to the ethereal filtrate or as free bases by removal of the ether under reduced pressure and subsequent vacuum distillation of the residue. The yields of purified N-benzylglycines ranged from 50 to 90%.

The acids **15** and **20** were obtained by refluxing a solution of 0.05 mole of the ethyl ester in 100 ml of 3 *N* hydrochloric acid for 3 hr. The solution was evaporated to dryness under reduced pressure and the crystalline residue was recrystallized from ethanol or methanol–benzene to give the hydrochloride of the acid in 75–85% yield.

2,3-Dihydro-4(1H)-isoquinolones 5 from N-Benzylglycine Ethyl Esters. General Procedure.—To 400 ml of sulfuric acid (80% by weight) was added cautiously 0.2 mole of the appropriate N-benzylglycine ethyl ester with external ice cooling. The resulting solution was kept at 100° for 4–6 hr, cooled to room temperature, and added slowly with stirring to 2 l. of ice-cold 6 *N* sodium hydroxide. The alkaline solution was extracted with three 200-ml portions of chloroform. The combined extracts were dried, filtered, and evaporated to dryness under vacuum. The 2,3-dihydro-4(1H)-isoquinolones were isolated either as free base (**29**) by crystallization of the residue or as crystalline hydrochlorides by solution of the residue in ether and addition of excess isopropyl alcoholic hydrogen chloride. After recrystallization from various solvents (see Table III), the purified crystalline amino ketones or their hydrochlorides were obtained in yields ranging from 10 to 65%.

N-(3-Methoxybenzyl)-N-benzylglycine Ethyl Ester (18).—To a solution of 13.96 g (0.1 mole) of glycine ethyl ester hydrochloride in 100 ml of methanol was added 6.8 g (0.1 mole) of sodium ethoxide dissolved in 310 ml of ethanol. The solvents were removed under vacuum, and the residue was suspended in dichloromethane. After removal of sodium chloride by filtration, the filtrate was evaporated to dryness under reduced pressure. The oily glycine ethyl ester was dissolved in 200 ml of absolute ethanol; a solution of 13.6 g (0.1 mole) of *m*-methoxybenzaldehyde in 200 ml of absolute ethanol was added, and the mixture was hydrogenated at room temperature and 10 atm over 2 g of platinum oxide until the hydrogen uptake ceased. After removal of the catalyst, the solvent was distilled under reduced pressure to give 19.5 g of residual yellow oil. To a solution of 3 g of this material in ether was added excess isopropyl alcoholic hydrogen chloride to give 2.8 g of crystalline hydrochloride which, after recrystallization from acetone, gave 2.1 g of pure **N-(3-methoxybenzyl)-glycine ethyl ester hydrochloride (14)**, mp 145–146°. A mixture melting point with material obtained by reaction of 3-methoxybenzylamine with ethyl chloroacetate according to the general method described above showed no depression.

A solution of 16 g (0.0717 mole) of crude **N-(3-methoxybenzyl)-glycine ethyl ester** and 10 ml (0.0717 mole) of triethylamine in 50 ml of anhydrous ether was added to a stirred solution of 8.25 ml (0.0717 mole) of benzylchloride in 50 ml of anhydrous ether. The mixture was refluxed and stirred for 50 hr. After removal of the precipitate by filtration, the filtrate was evaporated to dryness to give 25 g of a semicrystalline material, which was heated with a mixture of acetone and ether. The undissolved crystalline product (2.6 g of **14**) was removed by filtration, the filtrate was evaporated to dryness, and the residue was distilled to give 8.6 g (38%) of the N-benzylglycine ethyl ester **18**, bp

184° (0.75 mm). For comparison, 3 g of **18** was dissolved in ether, and addition of excess isopropyl alcoholic hydrogen chloride furnished 3.1 g of crystalline hydrochloride, mp 111–115°. Recrystallization from acetone–ether gave pure hydrochloride of **18**, mp 112–117°, which was identical by melting point and infrared spectral data with material prepared by reaction of **9** with ethyl chloroacetate according to the general method described above.

2,3-Dihydro-7-methoxy-4(1H)-isoquinolone Hydrochloride (26).—The hydrochloride of **29** was obtained by dissolving the free base in methanol and adding 1 *N* methanolic hydrochloric acid. After addition of ether, the hydrochloride precipitated as a crystalline product, mp 213–215°. The hydrochloride (10 g) was dissolved in 200 ml of glacial acetic acid by heating to 70°. After addition of the catalyst (1.2 g, 10% palladium on charcoal), the mixture was hydrogenated at room temperature under normal pressure until the theoretical amount of hydrogen, necessary for debenzylation, had been consumed. This required about 2.5 hr. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The solid residue was washed with ether to give 6.6 g (94%) of **26**, mp 220–222°. Recrystallization from methanol–ether gave 5.7 g (81%) of pure **26**: mp 224–225°; λ_{max} 225 mμ (ε 12,100), 229 (12,100), 287 (18,000); ν_{max}^{KBr} 2790, 2650, and 2500 (*sec*-amine salt), 1690 (C=O), and 1280 and 1250 cm^{-1} (OCH_3).

2,3-Dihydro-7-methoxy-1-methyl-4(1H)-isoquinolone Hydrochloride (30).—Hydrogenation of **32** under similar conditions gave **30** in 78% yield, mp 208–210° after recrystallization from ethanol. A sample was recrystallized several times from ethanol to give analytically pure **30**: mp 213–214°; λ_{max} 227 mμ (ε 11,750), 288 (16,900); ν_{max}^{KBr} 2760, 2660, and 2480 (*sec*-amine salt), 1700 (C=O), and 1280 and 1250 cm^{-1} (OCH_3).

2,3-Dihydro-6,7-dimethoxy-4(1H)-isoquinolone Hydrochloride (35).—Hydrogenation of **37** under the conditions described above afforded **35** in 94% yield: mp 237–238° after recrystallization from methanol; λ_{max} 235 mμ (ε 18,700), 280–281 (11,160), 316–317 (8650); $\lambda_{max}^{0.1\ N\ KOH}$ 226–227 mμ (ε 18,120), 264 (11,900), 277–278 (9710), 318 (7400); ν_{max}^{KBr} 2760, 2610, and 2510 (*sec*-amine salt), 1685 (C=O), and 1290 and 1260 cm^{-1} (OCH_3).

1,2,3,4-Tetrahydro-7-methoxy-4-isoquinolinol Hydrochloride (38).—A mixture of 1 g (3.74 mmoles) of the free base of **29** and 150 mg of 5% palladium on charcoal in 50 ml of glacial acetic acid was hydrogenated at normal pressure and room temperature until the hydrogen uptake ceased. Removal of the catalyst by filtration was followed by evaporation of the filtrate to dryness under vacuum. The oily residue was dissolved in ether and, upon addition of isopropyl alcoholic hydrogen chloride, crystalline **38** was obtained. Recrystallization from ethanol gave 500 mg (62%) of the isoquinolinol hydrochloride **38**: mp 168–170°; λ_{max} 227 mμ (ε 10,200), 277–278 (1750), 284 (1670); ν_{max}^{KBr} 3340 (OH), 2950, 2840 and 2670 (*sec*-amine salt), and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{10}H_{13}NO_2 \cdot HCl$ (215.67): C, 55.69; H, 6.54. Found: C, 56.01; H, 6.56.

1,2,3,4-Tetrahydro-7-methoxy-1-methyl-4-isoquinolinol Hydrochloride (39).—Hydrogenation of the free base of **32** as described in the preceding experiment gave **39** in 61% yield: mp 174–175° after recrystallization from ethanol; λ_{max} 228 mμ (ε 8900), 276 (1620), 284 (1480); ν_{max}^{KBr} 3320 (OH), 2780, 2660 and 2500 (*sec*-amine salt), and 1290 and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$ (229.72): C, 57.51; H, 7.02; N, 6.10. Found: C, 57.19; H, 7.19; N, 6.08.

Registry No.—**6**, 3459-14-1; **6** free base, 5071-96-5; **7**, 5071-92-1; **8**, 5120-82-1; **9**, 5077-16-7; **10**, 5077-14-5; **11**, 5077-11-2; **12**, 5077-08-7; **13**, 5077-05-4; **13** free base, 13174-24-8; **14**, 5071-94-3; **15**, 5071-93-2; **16**, 5071-91-0; **17**, 5077-21-4; **18**, 5077-15-6; **18** hydrochloride, 15297-11-7; **19**, 5077-20-3; **20**, 5077-19-0; **21**, 5077-13-4; **22**, 5077-18-9; **23**, 5077-10-1; **24**, 5077-06-5; **24** free base, 5077-07-6; **25**, 5077-04-3; **25** hydrochloride, 5120-80-9; **26**, 5119-79-9; **27**, 5071-90-9; **28**, 5120-83-2; **29**, 5120-75-2; **29** hydrochloride, 15297-22-0; **30**, 15297-23-1; **31**, 5120-81-0; **32**, 5077-12-3; **33**, 5077-17-8; **34**, 5077-09-8; **35**, 15297-27-5; **36**, 5489-51-0; **37**, 5077-03-2; **38**, 15297-30-5; **39**, 15297-31-1.

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Syntheses in the Isoquinoline Series. Synthesis and Chemical Transformation of 2,3-Dihydro-4(1H)-isoquinolones[1]

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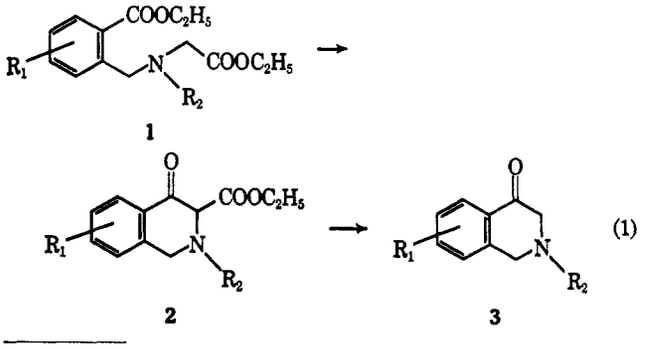
Several 2,3-dihydro-4(1H)-isoquinolones have been prepared by Dieckmann cyclization of suitable N-(*o*-carbalkoxybenzyl)glycine ester derivatives followed by hydrolysis and decarboxylation of the intermediate β-keto esters. The importance of these compounds as useful intermediates is shown by their conversion into various isoquinoline derivatives.

In the preceding paper we reported the preparation of 2,3-dihydro-4(1H)-isoquinolones by acid-catalyzed cyclization of suitably substituted N-benzylglycine esters.[2] In the 6,7-dimethoxy series this method gave poor results. Another route to 2,3-dihydro-4(1H)-isoquinolones consists of a Dieckmann cyclization of a diester followed by hydrolysis and decarboxylation of the intermediate β-keto ester. This synthetic scheme is illustrated (eq 1) by the conversion of **1** into **3** *via* **2** as reported by Hinton and Mann[3] where R_1 = H and R_2 = CH_3. The availability of a variety of substituted *o*-



(1) Presented in part by one of us (A. B.) before the section of Chemical Science at the New York Academy of Sciences, March 1966; *Trans. N. Y. Acad. Sci.*, [II] **28**, 685 (1966).

(2) G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968).

(3) I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959).