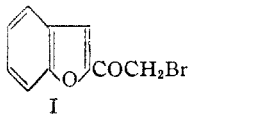
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohol Studies. 2,3-Dihydrobenzofuran Derivatives

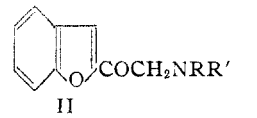
BY ALFRED BURGER AND ADOLPH J. DEINET

In continuation of a study of the significance of the cyclic ether linkage on the analgesic activity of compounds containing amino alcohol groups[1,2] we have now synthesized a number of amino alcohols derived from 2,3-dihydrobenzofuran. This ring system, with a secondary alcohol group attached to the 2-position, is present in morphine, and the placement of the amino alcohol chains in the compounds described in this article resembles more closely that found in the opium alkaloid, than that of similar derivatives of dibenzofuran and tetrahydrodibenzofuran previously reported.[3,4]

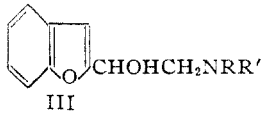
The starting material of our syntheses, 2-bromoacetylbenzofuran (I),[5] reacted smoothly in ether solution with a number of secondary amines, including diethylamine, morpholine, piperidine, dibenzylamine, and benzylmethylamine to yield the amino ketones II. Hydrogenation in the presence of Adams catalyst did not lead to homogeneous compounds, and more than one mole of hydrogen was absorbed in all cases. However, reduction of the amino ketone hydrochlorides with aluminum isopropoxide[2,6] furnished the corresponding alkamines III in yields ranging from 60 to 83%. The nuclear double bond between positions 2 and 3 was then saturated by hydrogenation in alcoholic hydrogen chloride solution under the influence of palladized charcoal. The resulting 2,3-dihydrobenzofuryl amino alcohols (IV) could also be obtained by hydrogenation over platinum but hydrogen absorption exceeded that calculated for one mole, the reaction had to be interrupted, and the yields were accordingly lower. Raney nickel in alcohol solution did not catalyze hydrogenation at atmospheric pressure.



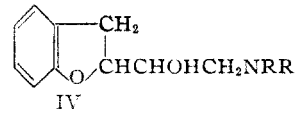
I



II



III



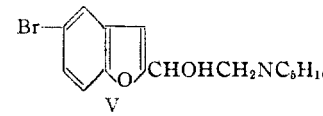
IV

In general, only one diastereoisomer of the amino alcohols IV was found but fractional crystallization of the hydrochloride of the piperidino alcohol (IV, $NR_2 = NC_5H_{10}$) afforded both racemic mixtures.

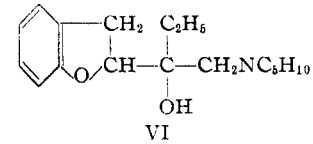
Hydrogenation of 1-(2-benzofuryl)-2-dibenzylamino ethanol [III, $-N(CH_2C_6H_5)_2$] proceeded much more rapidly than that of compounds with aliphatic or heterocyclic amino groups. After one mole of hydrogen was absorbed the rate of the reaction decreased to such an extent that it was possible conveniently to interrupt the reduction and to isolate the monobenzylamino alcohol formed (III, $-NHCH_2C_6H_5$). Further hydrogenation of this compound with palladium was slow, and only the nuclear double bond was saturated while the remaining benzyl group was not affected (IV, $-NHCH_2C_6H_5$). Likewise, hydrogenation of 2-dibenzylaminoacetyl benzofuran [II, $-N(CH_2C_6H_5)_2$] could be arrested readily after removal of one benzyl group (II, $-NHCH_2C_6H_5$). 2-Benzylmethylacetyl benzofuran [II, $-N(CH_3)CH_2C_6H_5$] also lost its benzyl group on catalytic hydrogenation and yielded 2-methylaminoacetylbenzofuran (II, $-NHCH_3$), while reduction by the Ponndorf–Meerwein–Verley method led to the expected benzylmethylamino alcohol [III, $-N(CH_3)CH_2C_6H_5$]. This compound absorbed one mole of hydrogen rapidly with the loss of its benzyl group, and another mole more slowly with the formation of the corresponding dihydrobenzofuryl methylamino alcohol (IV, $-NHCH_3$).

The ease with which one benzyl group is removed by hydrogenolysis of alkylbenzylamino or dibenzylamino ketones and alcohols in this series compares readily with similar observations by Baltzly and Buck[7] in the reductive elimination of benzyl groups from 2,5-dimethoxyphenyl benzylmethylamino ketones.

Nuclear halogen was more readily attacked by hydrogen on palladized charcoal than the furanoid double bond. 1-(5-Bromo-2-benzofuryl)-2-piperidino ethanol (V) lost its bromine atom in thirty seconds, and the halogen-free amino alcohol (III, $-NC_5H_{10}$) was isolated and identified.



V



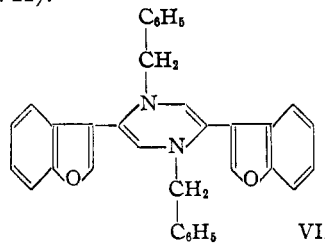
VI

As an example of a tertiary carbinol in the α-amino alcohol series we prepared 1-ethyl-1-(2-benzofuryl)-2-piperidinoethanol from 2-piperidinoacetylbenzofuran and ethylmagnesium iodide. The 2,3-double bond in this compound resisted hydrogenation catalyzed by palladium,

(1) Harnest and Burger, THIS JOURNAL, **65**, 370 (1943).
(2) Burger and Harnest, *ibid.*, **65**, 2382 (1943).
(3) Mosettig and Robinson, *ibid.*, **57**, 2186 (1935); **58**, 688 (1936).
(4) Kirkpatrick and Parker, *ibid.*, **57**, 1123 (1935).
(5) Shriner and Johnson, *ibid.*, **61**, 2705 (1939).
(6) *Cf.* Burger, Alfriend and Deinet, *ibid.*, **66**, 1327 (1944).
(7) Baltzly and Buck, *ibid.*, **62**, 164 (1940).

but could be saturated with hydrogen over platinum, the reduction being interrupted at this point (VI).

2-Benzylaminoacetylbenzofuran could not be prepared from the bromo ketone I and benzylamine. Gabriel[8] has pointed out the formation of pyrazine derivatives from primary amino ketones, and in a variation of his procedure we found that I and benzylamine form small amounts of 1,4-dihydro-1,4-dibenzyl-2,5-di-(2-benzofuryl)-pyrazine (VII).

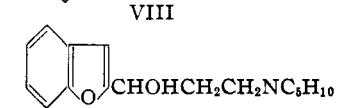


VII

While the condensation of α-halogeno ketones with primary amines may thus lead to dihydropyrazine derivatives, secondary amines should yield tertiary amino ketones only. However, non-basic materials that may contain nitrogen are often obtained besides, and sometimes even instead of the expected amino ketones.[9] In our earlier experiments the reaction of diethylamine and 2-bromoacetylbenzofuran yielded largely a yellow non-basic nitrogenous compound, and piperidine furnished a similar material but in smaller quantities. It was then found that the amount of these undesired by-products could be reduced by shortening the reaction time. Apparently, the dialkylamino ketone underwent a secondary reaction, perhaps with some of the unchanged bromo ketone. This view would explain why two chemically similar amines such as diethylamine and piperidine, with dissociation constants of the same order (diethylamine, 1.26×10^{-3}; piperidine, 1.6×10^{-3}) may react differently with the same α-halogeno ketone. Actually, the amino ketones first formed react at a different rate with one of the components of the reaction mixture.

A β-amino ketone (VIII) containing the piperidino group was obtained from 2-acetylbenzofuran by the Mannich reaction. The corresponding amino alcohol (IX), prepared by aluminum isopropoxide reduction, was hydrogenated in the presence of palladium to the coumaran derivative (X).

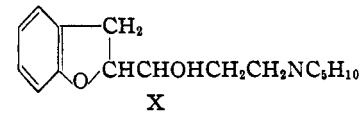
VIII



IX

(8) Gabriel, *Ber.*, **41**, 1127 (1908).

(9) (a) Burger and Bryant, THIS JOURNAL, **63**, 1054 (1941); (b) Cromwell and Cram, *ibid.*, **65**, 301 (1943).



X

The corresponding morpholino derivative was oily, and could not be characterized.

After completion of this work we learned about the article by Bergel, Haworth, Morrison and Rinderknecht[10] who started a program of synthetic analgesics with compounds related to those described in this paper. Among other derivatives, they prepared 2-(3-piperidinopropionyl)-7-methoxybenzofuran by a route analogous to that used by us in the synthesis of the amino ketones VIII.

The 2,3-dihydrobenzofuryl amino alcohols were tested by Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School, who found they exhibited only mild analgesic activity at almost toxic doses.

We wish to thank Smith, Kline and French Laboratories for aid in this investigation.

Experimental

Preparation of 2-Dialkylaminoacetylbenzofurans (II).—To an ice-cold mechanically stirred solution of 0.2 mole of the secondary amine in 250 cc. of dry ether was added a suspension of 0.1 mole (23.9 g.) of 2-bromoacetylbenzofuran[5] in 250 cc. of cold dry ether in several portions. Stirring at 0° was continued for one hour, and the mixture allowed to stand overnight at 25°. The crystalline precipitate of the amine hydrobromide was filtered with suction, the ethereal filtrate concentrated under reduced pressure, and the oily residue heated at 90° and 3 mm. for one hour in order to remove any unchanged amine.[11] The oily residue was dissolved in acetone, the solution filtered, and neutralized with ethereal hydrogen chloride. In general, the amino ketone hydrochlorides crystallized readily as colorless solids and were recrystallized from absolute ethanol–ether.

In the preparation of 2-diethylaminoacetylbenzofuran it was essential to stir the reaction mixture for not more than one hour at temperatures not exceeding 35°. The precipitated diethylammonium bromide was filtered, and the filtrate neutralized immediately with ethereal hydrogen chloride. Only in this manner a crystalline salt of the diethylamino ketone could be obtained. When the mixture was worked up according to the general directions mentioned above, a yellow non-basic material insoluble in acetone, m. p. 178°, was the main product isolated. Similar insoluble compounds appeared as side-products in small quantities in the preparation of some of the other amino ketones.

Preparation of 2-(1-Hydroxy-2-dialkylaminoethyl)-benzofurans (III).—One-tenth mole of the amino ketone hydrochloride was suspended in 100 cc. of 1 *M* aluminum isopropoxide solution diluted with an additional 150 cc. of dry isopropanol, and the mixture refluxed in the customary manner[2] for about six hours. The hydrochloride went gradually into solution. After the disappearance of acetone from the distillate, the solvent was removed under reduced pressure, and the residue shaken with 200 cc. of 12 *N* sodium hydroxide solution for about thirty minutes. The mixture was diluted with 200 cc. of water, the oily amino alcohol extracted into ether, the ether extract dried over sodium sulfate, and the solvent removed. The amino alcohols were usually converted to the hydrochlorides in acetone–ether solution, and the salts recrystallized

(10) Bergel, Haworth, Morrison and Rinderknecht, *J. Chem. Soc.*, 261 (1944).

(11) Morpholinoacetylbenzofuran crystallized on concentration of its ether solution.

from absolute alcohol–ether. In some cases, especially that of the diethylamino alcohol, it was advisable to distil the base at low pressures before neutralizing with ethereal hydrogen chloride.

Hydrogenation of 2-(1-Hydroxy-2-dialkylaminoethyl)-benzofurans to 2-(1-Hydroxy-2-dialkylaminoethyl)-2,3-dihydrobenzofurans (IV).—Palladium chloride (0.2 g.), dissolved in 10 cc. of warm saturated ethanolic hydrogen chloride was hydrogenated after addition of 40 cc. of ethanol and 1 g. of Darco. Five hundredths mole of the 2-(1-hydroxy-2-dialkylaminoethyl)-benzofuran hydrochloride, dissolved in 100 cc. of ethanol, was added to the suspension of the catalyst, and hydrogenated under atmospheric pressure. One mole of hydrogen was absorbed

TABLE I

Derivative of benzo[b]furan	M. p., °C.	Yield, %	Formula	Analyses, % Calcd.	Found
2-Diethylaminoacetyl-HCl	158.5	51	$C_{14}H_{17}NO_2 \cdot HCl$	Cl, 13.24	13.43
2-Piperidinoacetyl-HCl	222	75	$C_{15}H_{17}NO_2 \cdot HCl$	Cl, 12.67	12.72
Picrate	145.5		$C_{21}H_{20}N_4O_9$	N, 11.85	11.93
2-Morpholinoacetyl-HCl[a]	225–226	53	$C_{14}H_{18}NO_3 \cdot HCl$	Cl, 12.60	12.72
Picrate	171.5		$C_{20}H_{18}N_4O$	N, 11.83	12.65
2-Benzylaminoacetyl-HCl	222		$C_{17}H_{16}NO_2 \cdot HCl$	Cl, 11.75	11.71
2-Dibenzylaminoacetyl-HCl[b]	192	85	$C_{24}H_{21}NO_2 \cdot HCl$	Cl, 9.05	9.03
2-Benzylmethylaminoacetyl-HCl	184	52	$C_{18}H_{17}NO_2 \cdot HCl$	Cl, 11.23	11.23
2-Cyanoacetyl	148.5	84	$C_{11}H_7NO_3$	N, 7.57	7.84
5-Bromo-2-bromoacetyl-[c]	139	71	$C_{10}H_6Br_2O_2$	C, 37.79	37.74
				H, 1.93	2.41
5-Bromo-2-piperidinoacetyl-HCl[d]	215–217	78	$C_{15}H_{16}BrNO_2 \cdot HCl$	Cl, 9.89	9.80
2-Methylaminoacetyl-HCl	228		$C_{11}H_{11}NO_2 \cdot HCl$	Cl, 15.71	15.68
2-(3-Piperidinopropionyl)-HCl	197	43	$C_{16}H_{19}NO_3 \cdot HCl$	Cl, 12.07	11.96
2-(3-Morpholinopropionyl)-HCl	208	46	$C_{15}H_{17}NO_4 \cdot HCl$	Cl, 11.99	12.10
2-(1-Hydroxy-2-diethylaminoethyl)-HCl[e]	95	35	$C_{14}H_{19}NO_3 \cdot HCl$	Cl, 13.15	13.21
2-(1-Hydroxy-2-piperidinoethyl)-HCl	183	83	$C_{15}H_{19}NO_3 \cdot HCl$	Cl, 12.59	12.58
Picrate	141		$C_{21}H_{22}N_4O_9$	N, 11.83	12.28
2-(1-Hydroxy-2-morpholinoethyl)-HCl[f]	204	74	$C_{14}H_{17}NO_4 \cdot HCl$	Cl, 12.50	12.51
Picrate	181		$C_{20}H_{20}N_4O_{10}$	N, 11.78	11.08
2-(1-Hydroxy-2-dibenzylaminoethyl)-HCl[g]	185	84	$C_{24}H_{23}NO_3 \cdot HCl$	Cl, 9.01	8.96
2-(1-Hydroxy-2-benzylaminoethyl)-HCl	187.5	67	$C_{17}H_{17}NO_3 \cdot HCl$	Cl, 11.68	11.62
2-(1-Hydroxy-2-benzylmethylaminoethyl)-HCl	167.5	71	$C_{18}H_{19}NO_3 \cdot HCl$	Cl, 11.16	11.19
Picrate	141		$C_{24}H_{22}N_4O_9$	N, 10.98	11.01
2-(1-Hydroxy-2-methylaminoethyl)-picrate	205		$C_{17}H_{16}N_4O_9$	N, 13.34	13.67
5-Bromo-2-(1-hydroxy-2-piperidinoethyl)-HCl[h]	232	42	$C_{15}H_{18}BrNO_2 \cdot HCl$	Cl, 9.84	9.80
2-(1-Hydroxy-1-ethyl-2-piperidinoethyl)-HCl	161	38	$C_{17}H_{23}NO_2 \cdot HCl$	Cl, 12.35	12.30
2-(1-Hydroxy-3-piperidinopropyl)-HCl	138	22	$C_{16}H_{21}NO_2 \cdot HCl$	Cl, 12.00	12.10
2-(1-Hydroxy-3-morpholinopropyl)-HCl	170.5	46	$C_{15}H_{19}NO_3 \cdot HCl$	Cl, 11.90	11.93
2,3-Dihydro-2-(1-hydroxy-2-diethylaminoethyl)-picrate[i]	132		$C_{20}H_{24}N_4O_9$	N, 12.09	13.09
2,3-Dihydro-2-(1-hydroxy-2-piperidinoethyl)HCl	178	50	$C_{15}H_{21}NO_2 \cdot HCl$	Cl, 12.50	12.53
				H, 7.81	7.74[j]
soluble diastereoisomer	214		$C_{15}H_{21}NO_2 \cdot HCl$	Cl, 12.50	12.48
				C, 63.61	63.61
				H, 7.81	8.39
2,3-Dihydro-2-(1-hydroxy-2-morpholinoethyl)-HCl	191	70	$C_{14}H_{17}NO_3 \cdot HCl$	Cl, 12.41	12.40
				C, 58.90	57.71
				H, 7.05	7.18
2,3-Dihydro-2-(1-hydroxy-2-benzylaminoethyl)-HCl	214.5	70	$C_{17}H_{19}NO_3 \cdot HCl$	Cl, 11.62	11.59
				C, 66.80	66.55
				H, 6.59	6.15
2,3-Dihydro-2-(1-hydroxy-2-methylaminoethyl)-HCl	187	69	$C_{11}H_{15}NO_3 \cdot HCl$	Cl, 15.46	15.61
				C, 57.60	57.34
				H, 7.05	6.95
2,3-Dihydro-2-(1-hydroxy-3-piperidinopropyl)-HCl	176		$C_{16}H_{23}NO_2 \cdot HCl$	Cl, 11.90	11.98
				C, 64.71	64.98
				H, 8.11	8.25
2,3-Dihydro-2-(1-hydroxy-1-ethyl-2-piperidinoethyl)-picrate[k]	156		$C_{22}H_{28}N_4O_9$	N, 11.40	11.74

[a] Free base, m. p. 101.5°. [b] Free base, m. p. 155°. [c] Prepared from 5-bromosalicylaldehyde and chloroacetone and subsequent bromination. [d] Prepared from 5-bromo-2-bromoacetylbenzofuran and piperidine in ether solution. [e] Recrystallized from ethyl acetate. The free base showed b. p. 150–151° (3 mm.), $n^{20}D$ 1.5430. [f] Free base, m. p. 82°, b. p. 210° (8 mm.). [g] Free base, m. p. 181°. [h] From 5-bromo-2-piperidinoacetylbenzofuran hydrochloride with aluminum isopropoxide. [i] Free base, b. p. 159–161° (3 mm.), $n^{20}D$ 1.5283. [j] The C-value was consistently lower than the calculated one. [k] The oily free base was prepared from 2-(1-hydroxy-1-ethyl-2-piperidinoethyl)-benzofuran by hydrogenation with platinum oxide in ethanol solution under atmospheric pressure, and purified by slow distillation at 1 mm.

generally within ten to twelve hours. The catalyst was filtered and the solution evaporated to dryness under reduced pressure. With the exception of the diethylamino derivative, all the dihydrobenzofuran amino alcohol hydrochlorides appeared as colorless solids, and were recrystallized from absolute alcohol–ether.

Debenzylation Experiments.—Hydrogenolysis of the hydrochlorides of 2-dibenzylaminoacetylbenzofuran [II, $-N(CH_2C_6H_5)_2$] to 2-benzylaminoacetylbenzofuran (II, $-NHCH_2C_6H_5$), of 2-benzylmethylaminoacetylbenzofuran [II, $-N(CH_3)CH_2C_6H_5$] to 2-methylaminoacetylbenzofuran (II, $-NHCH_3$), of 1-(2-benzofuryl)-2-dibenzylamino-ethanol [III, $-N(CH_2C_6H_5)_2$] to 1-(2-benzofuryl)-2-benzylaminoethanol (III, $-NHCH_2C_6H_5$), and of 1-(2-benzofuryl)-2-benzylmethylaminoethanol [III, $-N(CH_3)CH_2C_6H_5$] to 1-(2-benzofuryl)-2-methylaminoethanol (III, $-NHCH_3$) was carried out with prereduced palladized charcoal under the same conditions as those described above for the preparation of the 2,3-dihydrobenzofuran amino alcohols (IV). The time required for the debenzylation of 1 g. samples varied from two to thirty minutes.

2-(1-Ethyl-1-hydroxy-2-piperidino)-benzofuran.—A solution of 8.5 g. of 2-piperidinoacetylbenzofuran in 150 cc. of dry benzene was added gradually to a stirred ice-cold solution of ethylmagnesium iodide prepared from 1.7 g. of magnesium and 11.6 g. of ethyl iodide in 20 cc. of dry ether. After completion of the addition, the ether was distilled off, the mixture refluxed for two hours, and hydrolyzed with 20 g. of ice and 45 cc. of a cold 25% ammonium chloride solution. The tertiary alcohol was extracted into benzene, the extract dried over sodium sulfate, the solvent distilled under reduced pressure, and the oily residue converted to the hydrochloride.

2-(3-Piperidinopropionyl)-benzofuran.—A mixture of 25.5 g. of 2-acetylbenzofuran, 25 g. of piperidine hydrochloride, 6.7 g. of paraformaldehyde, 50 cc. of isoamyl alcohol, and four drops of ethanolic hydrogen chloride was refluxed for two minutes when the amino ketone hydrochloride precipitated. After cooling, it was filtered and recrystallized from ethanol.

Reduction of the β-piperidino ketone hydrochloride with aluminum isopropoxide was carried out as described above for the series of α-amino ketones. Likewise, hydrogenation of the β-piperidino alcohol with palladized charcoal followed the pattern set for the lower homologs.

1,4-Dibenzyl-1,4-dihydro-2,5-di-(2-benzofuryl)-pyrazine.—A solution of 3 g. of 2-bromoacetylbenzofuran in 35 cc. of dry benzene was added slowly to a solution of 2 g. of benzylamine in 15 cc. of benzene. After standing for ten hours at room temperature, the precipitated benzylammonium bromide was filtered, the solvent removed from the filtrate *in vacuo*, and the residue heated at 100° and 1 mm. for thirty minutes. It was dissolved in ether, the solution filtered from much tar, and neutralized with ethereal hydrogen chloride. The tan dihydrochloride, crystallized from ethanol–ether, melted at 220°. The yield was 0.5 g.

Anal. Calcd. for $C_{44}H_{36}N_2O_2 \cdot 2HCl$: Cl, 12.5. Found: Cl, 12.1.

2-Cyanoacetylbenzofuran.—A suspension of 12 g. of 2-bromoacetylbenzofuran in 60 cc. of ethanol was added to a solution of 9 g. of sodium cyanide in 30 cc. of water. The temperature rose to 50°. After stirring at 50–55° for one-half hour, the mixture was cooled, diluted with 100 cc. of water, filtered with the aid of Darco, and the filtrate acidified with concentrated hydrochloric acid. The cyano ketone separated out. The yellow crystals were filtered, washed, and recrystallized from acetone.

One-half gram of the cyano ketone was cleaved by boiling with 25 cc. of a 3% potassium hydroxide solution for two hours until no more ammonia was evolved. The solution was cooled, acidified, and the white precipitate of benzofuran-2-carboxylic acid filtered, washed and dried. It melted at 191°, and a mixture melting point with a sample of coumarilic acid showed no depression.

Color Reactions.—The dialkylamino ketones and alcohols described in this article exhibited distinctive color reactions with cold concentrated sulfuric acid. The amino ketones II and VIII gave a deep yellow, the amino alcohols III a deep blue, the amino alcohols IX a deep green, and the coumaran derivatives IV and X a deep red color. The corresponding dibenzylamino compounds showed the same color reactions but in a much less marked degree.

Summary

The synthesis of a number of 2,3-dihydrobenzofuryl amino alcohols containing secondary and tertiary alcohol and amino groups has been described. Certain side-reactions encountered in the course of the syntheses have been discussed.

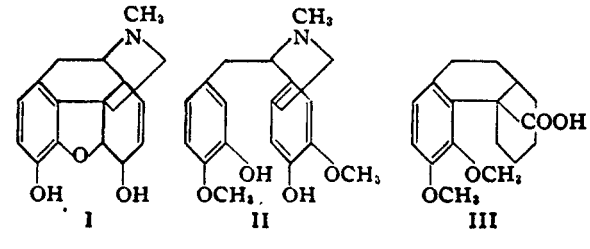
CHARLOTTESVILLE, VA. RECEIVED OCTOBER 23, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Experiments on the Synthesis of Compounds Related to Morphine. I. The Internal Michael Reaction

BY C. F. KOELSCH

Although twenty years have elapsed since the proposal of an adequate structure for morphine (I)[1] little progress has been made toward the synthesis of this important alkaloid. A projected synthesis of a portion of the morphine molecule by Manske[2] was abandoned in its early stages. Researches by Robinson and co-workers[3] were directed toward morphine through bases of the laudanosine type, but the hoped for "fortunate and partly fortuitous discovery" of a way to transform these substances (*e. g.*, "protosinomenine," II) into phenanthrene alkaloids has not yet been made. Experiments by Schöpf and co-



(1) Gulland and Robinson, *Mem. Manchester Phil. Soc.*, **69**, 79 1925).

(2) Manske, THIS JOURNAL, **53**, 1104 (1931).

(3) Robinson and Sugasawa, *J. Chem. Soc.*, 3163, 3173 (1931); 789 (1932); 280 (1933); Kitasato and Robinson, *ibid.*, 785 (1932).