non-ionic chromium takes place independently of the carboxyl group of collagen, is provided by unpublished data on the interaction of modified polyamides with the two forms of chromium complexes. A hydrated, modified polyamide was prepared from a copolymer of hexamethylene–adipic acid salt and caprolactam, by turbining a 3% hot methanol solution of the polyamide into water. The content of anionic groups (carboxylic end groups) was 0.02 milliequiv. per g. of polyamide or less than 2% of the number of carboxyls of collagen. The main functional group is the –CO–NH– link, part of the same possessing free coördination sites. Its coordination potency is evident from the fact that the modified polyamide exceeds collagen in its binding capacity for polyphenols (tannic acid). The sulfito complexes are not suitable reactants on account of their high degree of aggregation, their diffusion into the polyamide being obstructed. Solutions of chromium perchlorates were used. From solutions of the 33% acid chromium perchlorate, which contained 32% cationic and 68% non-ionic complexes, the polyamide fixed 7.2% Cr_2O_3, figured on its original weight. In corresponding series with purely cationic chromium complexes of the 75% acid perchlorate, no reaction was evident, neither with the basic chromium sulfate (no. 1 of Table I); thus proving the –CO–NH–link to be the functional group of the polyamide for its combination with non-ionic chromium complexes.

The present findings prove the exclusive function of the carboxyl ions of collagen for the initial attraction of electropositive chromium complexes and for the final irreversible fixation of these complexes by collagen, the high complexing power of the carboxyl group directing the ultimate attachment. Further, they disprove the supposed versatility of the carboxyl group in binding all types of chromium irrespective of their sign of charge and composition; a view held by Shuttleworth.[4] The great avidity of collagen lacking in carboxyl groups for non-cationic complexes and the array of earlier findings proving this type of chrome fixation to be governed by the degree of availability of non-ionic protein groups, and hence to be a function of the nature of the pretreatments of collagen, unequivocally provide evidence for the participation of groups other than the carboxylic group in the binding of non-cationic chromium complexes by hide protein.

Acknowledgment.—A research grant from the *Swedish Technical Research Council* is gratefully acknowledged. The author wishes to express his gratitude to Miss B. Holm and Miss K. Dahlgren for invaluable assistance.

STOCKHOLM, SWEDEN

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

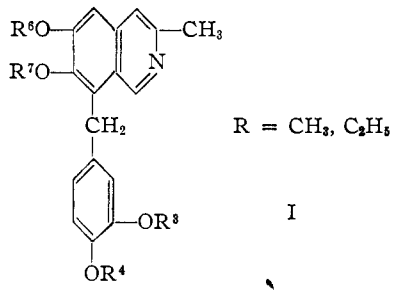
Papaverine Homologs. III. The Preparation of Some 3-Methylisoquinolines[1]

BY EDWIN R. SHEPARD, JOHN F. NOTH, HERSCHEL D. PORTER AND CLAUDENE K. SIMMANS

RECEIVED MARCH 26, 1952

The investigation of papaverine-like isoquinolines has been extended to the 3-methyl compounds (I). During the course of preparing the intermediate phenylisopropylamines, two methods of synthesis were investigated more fully. Three of the isoquinolines have shown unusual pharmacological activity. One of these, 6,7-dimethoxy-1-(4′-ethoxy-3′-methoxy)-3-methylisoquinoline, has been examined clinically.

In view of the results which were obtained upon investigation of the methoxy-ethoxy homologs of papaverine for their coronary dilator action,[2] it was felt to be desirable to prepare the corresponding 3-methyl homologs (I) for comparative

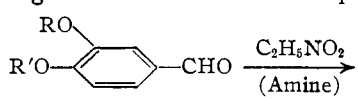


R = CH_3, C_2H_5

I

pharmacological evaluation. The previous literature had indicated that the 3-methylisoquinolines were effective as antispasmodics on smooth muscle.[3] However, since we had found that the antispasmodic action on isolated muscle did not parallel the coronary dilator action in a quantitative sense, there was no sound basis for predicting the activity of the 3-methylisoquinolines as coronary dilators.

The synthetic route followed for the preparation of this group of compounds (I) was essentially the same as that previously reported, with the exception of the preparation of the intermediate amines. For this latter purpose the condensation of the various 3,4-dialkoxybenzaldehydes with nitroethane to yield the corresponding 1-(3,4-dialkoxyphenyl)-2-nitro-1-propenes was quite attractive since the alkoxy substituents could be varied readily to provide ultimately the prerequisite 1-(3,4-dialkoxyphenyl)-isopropylamines. The yields upon examination of the literature seemed promising for the entire series of steps[4–6]



(1) Paper II of this series: E. R. Shepard, H. D. Porter, J. F. Noth and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

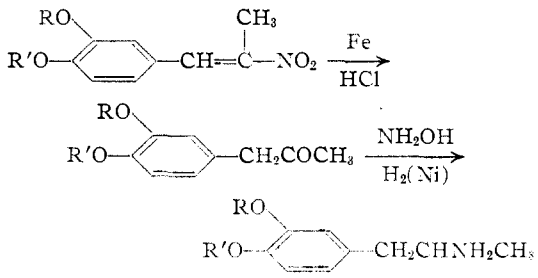
(2) E. R. Shepard and J. F. Noth, THIS JOURNAL, **72**, 4364 (1950).

(3) F. T. v. Brücke and H. Jesserer, *Arch. expll. Path. Pharmakol.*, **190**, 515 (1938); H. Kreitmair, *ibid.*, **164**, 509 (1932).

(4) H. Kauffmann, *Ber.*, **52**, 1431 (1919).

(5) A. G. Susie, Ph.D. Thesis, Purdue University, 1939.

(6) H. Adkins and C. F. Winans, THIS JOURNAL, **55**, 2051 (1933).



Since nitroparaffins condense with aromatic aldehydes under a variety of conditions, several modifications of Kauffmann's method for the preparation 1-(3,4-dimethoxyphenyl)-2-nitro-1-propene were tried. When piperidine, triethylamine, aniline or Triton B was used as the condensing agent, no nitropropene could be isolated. On the other hand, a variety of primary alkyl and aralkylamines, namely, butylamine, decylamine, benzylamine and phenethylamine, gave satisfactory results. Additionally, it was observed that the reaction was unusual since the molar quantity of primary amine required to produce optimum yields of the nitropropene had a specific value above and below which the yields diminished. This situation is illustrated in Fig. 1 for a one-tenth mole scale reaction.[7]

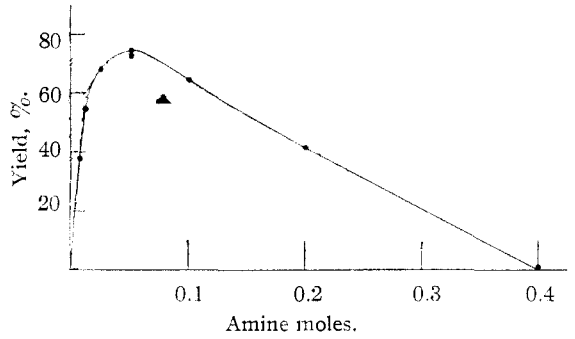
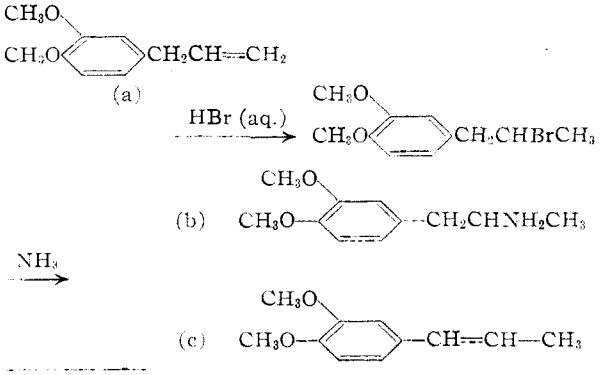


Fig. 1.—Yield dependence on the moles of condensation agent (●, *n*-butylamine; ■, *n*-decylamine; ▲, benzylamine) used per mole of veratraldehyde and 1.1 moles of nitroethane. Reacted at room temperature (25–30°) for 11 days on a one-tenth mole scale.

An alternate path to the preparation of the amine was afforded by the reaction of ammonia with the appropriate dialkoxyphenylisopropyl bromide.[8] The latter were obtained by addition of hydrogen bromide to the corresponding 1-(dialkoxyphenyl)-2-propenes. The patent covering this process indicated that the low conversion had compensation in recovery of a propene identical with the starting material. Thus a recycling to give a satisfactory over-all yield was indicated. The reaction was therefore examined, starting with eugenol methyl ether.



The yield of crude bromopropane was quantitative. However, the reaction with ammonia under a variety of conditions gave the expected amine (b) in approximately 35% yield, a 30% yield of higher boiling basic and neutral oils, and approximately 35% of an unsaturated substance which proved to be isoeugenol methyl ether (c), not the initial ether (a). It would thus appear that this elimination reaction follows the more usual course for 2-halogen substituted hydrocarbons.

The reactions of the acids with the amines to yield the various amides, and their ultimate conversion to the respective 3-methylisoquinoline salts, were conducted as described in the previous studies.[1,2] Several of the amides (Table I) derived from 1-(3',4'-diethoxyphenyl)-isopropylamine could not be recrystallized in such a way as to obtain satisfactory melting points. This difficulty was eventually ascribed to a very small degree of relatively stable solvation of these amides. The amide analyses, the preparation of isoquinolines of satisfactory melting points from the amides and, finally, the preparation of an unrecrystallized amide of much narrower melting range by fusion of an acid and the amine confirmed this interpretation.

The phosphate salt of 6,7-dimethoxy-1-(4'-ethoxy-3'-methoxy)-benzyl-3-methylisoquinoline proved to be unusual. When equimolar amounts of the base and phosphoric acid were mixed in ethanol, the salt with one and a half moles of phosphate per mole of base separated. The remaining base precipitated on dilution of the mother liquor with water. The base was electrometrically titrated and found to be normal, pK_a' being 5.8 in water and 5.80 in 43% dimethylformamide, compared with pK_a' of 5.47 for papaverine in dimethylformamide solution. Salt formation of this sort is not general, although in reporting the diphosphate salt of berberine, Shedden indicated that other similar cases involving phosphate salts have been observed.[9]

The isoquinoline salts were examined for their coronary dilator and smooth muscle antispasmodic actions. Compounds 10 and 15 (Table III) were unique in that they were not only approximately equal to papaverine as coronary dilators but they also possessed a marked antispasmodic action on smooth muscle. Compound 5 (Table III), as the phosphate and the hydrochloride, has been examined extensively.[10] It has proved to be somewhat more effective than papaverine as a coronary dilator and is noteworthy because of its low order of toxicity and absence of other significant pharmacological side effects.

(7) The same approximate relationships have been observed on larger runs although it has been found that mole yield values could not be translated quantitatively.

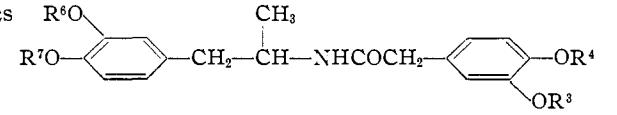
(8) German Patent 274,350 (1914).

(9) F. Shedden, *Pharm. J.*, (iv), **11**, 89 (1900).

(10) F. G. Henderson, R. E. Shipley and K. K. Chen, *J. Am. Pharm. Assoc. Sci. Ed.*, **11**, 207 (1951).

TABLE I

N-(α-METHYLPHENETHYL)-PHENYLACETAMIDES

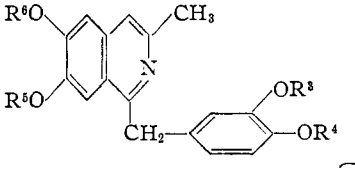


R³	R⁴	R⁶	R⁷	M.p., °C.	Yield, %	Formula	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	CH_3	CH_3	126.5–127.5	85	$C_{21}H_{27}NO_5$	67.54	67.29	7.28	7.01
CH_3	CH_3	CH_3	C_2H_5	120–121	81	$C_{22}H_{29}NO_5$	68.19	67.93	7.54	7.30
CH_3	CH_3	C_2H_5	C_2H_5	124–125[b]	76	$C_{23}H_{31}NO_5$	68.80	68.65	7.78	7.70
CH_3	CH_3	C_2H_5	CH_3	128–128.5	80	$C_{22}H_{29}NO_5$	68.19	68.15	7.54	7.77
CH_3	C_2H_5	CH_3	CH_3	135–136	84	$C_{22}H_{29}NO_5$	68.19	68.05	7.54	7.62
CH_3	C_2H_5	CH_3	C_2H_5	97.5–98[c]	77	$C_{23}H_{31}NO_5$	68.80	68.48	7.78	7.59
CH_3	C_2H_5	C_2H_5	CH_3	135–136.5	76	$C_{23}H_{31}NO_5$	68.80	68.69	7.78	7.96
CH_3	C_2H_5	C_2H_5	C_2H_5	121–128	74	$C_{24}H_{33}NO_5$	69.36	69.48	8.01	8.09
C_2H_5	CH_3	CH_3	CH_3	101.5–102.5	67	$C_{22}H_{29}NO_5$	68.19	67.92	7.54	7.70
C_2H_5	CH_3	CH_3	C_2H_5	124–125	78	$C_{23}H_{31}NO_5$	68.80	68.55	7.78	7.61
C_2H_5	CH_3	C_2H_5	CH_3	126.5–127.5	76	$C_{23}H_{31}NO_5$	68.80	68.55	7.78	8.07
C_2H_5	CH_3	C_2H_5	C_2H_5	117–119[d]	68	$C_{24}H_{33}NO_5$	69.36	69.35	8.01	7.82
C_2H_5	C_2H_5	CH_3	CH_3	66–67[c]	78	$C_{23}H_{31}NO_5$	68.80	68.86	7.78	7.62
C_2H_5	C_2H_5	CH_3	C_2H_5	100–101	86	$C_{24}H_{33}NO_5$	69.36	69.14	8.01	7.85
C_2H_5	C_2H_5	C_2H_5	CH_3	118–119[e]	70	$C_{24}H_{33}NO_5$	69.36	69.00	8.01	7.98
C_2H_5	C_2H_5	C_2H_5	C_2H_5	97–102	61	$C_{25}H_{35}NO_5$	69.91	69.90	8.21	8.29

[a] All analyses, dried at 80° over phosphorus pentoxide *in vacuo* unless otherwise indicated. [b] The crude, m.p. 121–123.5°, recrystallized twice from dilute alcohol and dried at 90° overnight, m.p. 118–124°. [c] From dilute methanol followed by recrystallization from Skellysolve B and benzene. Dried at 56° over phosphorus pentoxide *in vacuo* for 4 hours. [d] From Skellysolve B and then from dilute methanol, dried overnight at 90°, m.p. 107–119°. [e] From dilute methanol followed by recrystallization from ethyl acetate–Skellysolve. Evidence of an unstable hydrate (or methanolate), m.p. 128–130°, was obtained in one series of three crystallizations from dilute aqueous methanol.

TABLE II

ISOQUINOLINES



No.	R³	R⁴	R⁶	R⁷	M.p., °C.	Yield %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	CH_3	CH_3	CH_3	CH_3	138–138.5	78	$C_{21}H_{23}NO_4$	71.36	71.24	6.55	6.55
2	CH_3	CH_3	CH_3	C_2H_5	131.5–133	74	$C_{22}H_{25}NO_4$	71.91	72.08	6.85	7.01
3	CH_3	CH_3	C_2H_5	C_2H_5	148.5–149.5	87	$C_{23}H_{27}NO_4$	72.41	72.22	7.13	7.38
4	CH_3	CH_3	C_2H_5	CH_3	129.5–130	81	$C_{22}H_{25}NO_4$	71.91	72.01	6.85	6.90
5	CH_3	C_2H_5	CH_3	CH_3	126–126.5	83	$C_{22}H_{25}NO_4$	71.91	71.68	6.85	7.07
6	CH_3	C_2H_5	CH_3	C_2H_5	127.5–128.5	75	$C_{23}H_{27}NO_4$	72.41	72.29	7.13	7.26
7	CH_3	C_2H_5	C_2H_5	CH_3	123.5–124.5	25[b]	$C_{23}H_{27}NO_4$	72.41	72.10	7.13	7.11
8	CH_3	C_2H_5	C_2H_5	C_2H_5	148.5–150	22	$C_{24}H_{29}NO_4$	72.88	72.80	7.39	7.20
9	C_2H_5	CH_3	CH_3	CH_3	148–149.5[a]	54[b]	$C_{22}H_{25}NO_4$	71.91	71.57	6.85	6.80
10	C_2H_5	CH_3	CH_3	C_2H_5	122–124	90	$C_{23}H_{27}NO_4$	72.41	72.53	7.13	7.42
11	C_2H_5	CH_3	C_2H_5	CH_3	144–145	77	$C_{23}H_{27}NO_4$	72.41	72.09	7.13	7.19
12	C_2H_5	CH_3	C_2H_5	C_2H_5	128–129	45[b]	$C_{24}H_{29}NO_4$	72.88	72.93	7.39	7.41
13	C_2H_5	C_2H_5	CH_3	CH_3	105–105.5	73	$C_{23}H_{27}NO_4$	72.41	72.43	7.13	7.25
14	C_2H_5	C_2H_5	CH_3	C_2H_5	112.5–113.5	83	$C_{24}H_{29}NO_4$	72.88	73.11	7.39	7.49
15	C_2H_5	C_2H_5	C_2H_5	CH_3	116–117	79	$C_{24}H_{29}NO_4$	72.88	72.88	7.39	7.42
16	C_2H_5	C_2H_5	C_2H_5	C_2H_5	120–121[c]	44[b]	$C_{25}H_{31}NO_4$	73.32	73.14	7.63	7.74

[a] Recrystallized twice from dilute ethanol. It melted at 64–65.5°, resolidified and remelted at 148–149.5°. [b] Isolated as the hydrochloride. [c] V. Bruckner, G. Fodor, J. Kiss and J. Kovacs, *J. Chem. Soc.*, 885 (1948), m.p. 117–118°.

Experimental

1-(3′-Ethoxy-4′-methoxyphenyl)-2-nitro-1-propene.—One hundred forty-eight grams (0.82 mole) of 3-ethoxy-4-methoxybenzaldehyde was dissolved in 61.5 g. (0.82 mole) of nitroethane. After cooling, 8 ml. of *n*-butylamine was stirred in and the mixture was stored in a stoppered flask for 11 days. The resulting mixture of solid and liquids was dissolved in approximately 400 ml. of ethanol. Crystals were obtained upon cooling and seeding the solution. After standing several hours at 0°, the yellow needles were filtered and washed with cold 50% (vol.) alcohol to yield 153.5 g. (78%), m.p. 80.5–81.5°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.64; H, 6.25; N, 5.79.

1-(4′-Ethoxy-3′-methoxyphenyl)-2-nitro-1-propene.—Two moles of 4-ethoxy-3-methoxybenzaldehyde and two moles of nitroethane were treated with 20 ml. of butylamine as in the foregoing example. Three hundred fifty-five grams (75%) of the propene was obtained, m.p. 111.5–112°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.51; H, 6.21; N, 5.69.

1-(3′,4′-Dimethoxyphenyl)-2-nitro-1-propene.—Prepared in an analogous manner. A 75% yield of the propene, m.p. 73.5–74.5°, was obtained (lit.[4] 73°).

TABLE III

ISOQUINOLINE SALTS

Salt of base no.	Formula	M.p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	$C_{21}H_{23}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O$[a]	236.5-237.5	63.99	64.21	6.59	6.14
2	$C_{22}H_{25}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O$	202-208	64.70	64.56	6.85	7.23
3	$C_{23}H_{27}NO_4 \cdot HCl$	192-197	66.09	65.82	6.75	6.83
4	$C_{22}H_{25}NO_4 \cdot HCl$	199-202	65.42	65.36	6.49	6.56
5	$C_{22}H_{25}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O$	211-213	64.70	64.50	6.85	6.61
	$C_{22}H_{25}NO_4 \cdot HBr$	220-223	58.93	58.80	5.84	6.04
	$C_{22}H_{25}NO_4 \cdot 1{}^1/_2H_3PO_4 \cdot {}^1/_2H_2O$	197-199	50.48	50.75	5.87	5.91
6	$C_{23}H_{27}NO_4 \cdot HCl$	200-202	66.09	65.92	6.75	6.92
7	$C_{23}H_{27}NO_4 \cdot HCl \cdot {}^1/_2H_2O$	201-205	64.70	64.53	6.85	6.48
8	$C_{24}H_{29}NO_4 \cdot HCl \cdot {}^1/_2H_2O$	189-196[b]	65.37	65.33	7.09	7.02
9	$C_{22}H_{25}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O \cdot {}^1/_2H_2O$	180-184	63.36	63.25	6.94	7.16
10	$C_{23}H_{27}NO_4 \cdot HCl$	221-222	66.09	65.83	6.75	6.94
11	$C_{23}H_{27}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O \cdot H_2O$	182.5-183.5	62.80	63.00	7.24	7.46
12	$C_{24}H_{29}NO_4 \cdot HCl \cdot {}^1/_2H_2O$	176-180	65.37	65.02	7.09	7.29
13	$C_{23}H_{27}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O$	179-183	65.37	65.29	7.09	6.69
14	$C_{24}H_{29}NO_4 \cdot HCl$	204-208	66.73	66.55	7.00	7.34
15	$C_{24}H_{29}NO_4 \cdot HCl \cdot {}^1/_2C_2H_6O$	200-201	66.00	66.16	7.31	7.02
16	$C_{25}H_{31}NO_4 \cdot HCl$	182-189	67.33	67.30	7.23	7.41

[a] C_2H_6O, ethanol of crystallization. [b] Softened at 175-178°, and resolidified before melting.

1-(3',4'-Diethoxyphenyl)-2-nitro-1-propene.—A mixture of 202.0 g. (1.04 moles) of 3,4-diethoxybenzaldehyde, 78.0 g. (1.04 moles) of nitroethane and 11.0 ml. of butylamine reacted as in the previous examples. A probe of the resultant oil layer was diluted with ethanol and chilled in a Dry Ice–acetone-bath to induce crystallization. The main reaction mixture was then crystallized from dilute aqueous ethanol at −20° to yield 122.0 g. (44%) of the propene, m.p. 59–60°.[11] Recrystallization did not change the melting point.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.58. Found: C, 62.14; H, 7.01; N, 5.71.

1-(3',4'-Diethoxyphenyl)-2-propanone.—A mixture of 195.0 g. (3.5 moles) of iron filings (30 mesh), 370.0 ml. of water, 122.0 g. (0.48 mole) of 1-(3',4'-diethoxyphenyl)-2-nitro-1-propene and 0.5 g. of ferric chloride was refluxed under vigorous stirring as 71.0 ml. (0.85 mole) of concentrated hydrochloric acid was dropped in during the course of 70 minutes. Heating and stirring were continued for six hours after the addition of acid. The cooled reaction mixture was stirred with 500 ml. of benzene and approximately 50 g. of a non-caking filter-aid (Hyflo Super-Cel). The mixture was filtered and the filter cake was rinsed well with benzene. The benzene layer of the filtrate was washed once with dilute hydrochloric acid and twice with water. The wet benzene solution was fractionated twice to obtain 91.8 g. (85%) of the ketone, b.p. 125–130° (0.28 mm.), $n^{27}D$ 1.5158.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.15; H, 8.16. Found: C, 70.20; H, 7.99.

Since the yield of the starting propene was poor, a reduction of the crude nitropropene reaction mixture was attempted, assuming 100% conversion to nitropropene. Based on the starting aldehyde, a 77% yield of the propanone was obtained, suggesting rather poor isolation of the intermediate nitropropene.

The following propanones were obtained in an analogous manner from the corresponding crystalline nitropropenes:

1-(3'-Methoxy-4'-ethoxyphenyl)-2-propanone.—B.p. 129–135° (0.25 mm.), $n^{27.5}D$ 1.5256, yield 90%.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.05; H, 7.57.

1-(3'-Ethoxy-4'-methoxyphenyl)-2-propanone.—B.p. 152–154° (6.0 mm.), $n^{25.5}D$ 1.5255, yield 81%.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.01; H, 7.99.

1-(3',4-Dimethoxyphenyl)-2-propanone.—B.p. 129–133° (0.4 mm.), $n^{25.5}D$ 1.5331, yield 82%.[12]

1-(3',4'-Dimethoxyphenyl)-2-propanone Oxime.—A mixture of 150 g. (0.77 mole) of 1-(3',4'-dimethoxyphenyl)-2-propanone, 125 ml. of water and 70 g. (1.01 moles) of hydroxylamine hydrochloride was stirred while 51.3 g. (0.48 mole) of sodium carbonate in 150 ml. of water was added during the course of 15 minutes. The mixture was stirred for an additional 2.5 hours. The product was taken up in ether, washed with water and fractionated to yield 151 g. (93%) of the oxime, b.p. 165–175° (0.6 mm.). Contrary to expectations,[13] the oxime could not be induced to crystallize. The following propanone oximes were obtained in an analogous manner.

1-(3',4'-Diethoxyphenyl)-2-propanone Oxime.—B.p. 155–165° (0.4 mm.), $n^{25}D$ 1.5442, yield 92%.

Anal. Calcd. for $C_{13}H_{19}NO_3$: N, 5.90. Found: N, 5.60.

1-(3'-Ethoxy-4'-methoxyphenyl)-2-propanone Oxime.—B.p. 165–175° (0.5 mm.), $n^{25}D$ 1.5461, yield 89%.

Anal. Calcd. for $C_{12}H_{17}O_3$: N, 6.27. Found: N, 6.20.

1-(4'-Ethoxy-3'-methoxyphenyl)-2-propanone Oxime.—The reaction product was washed by decantation and crystallized twice from a mixture of ethyl acetate and hexane. A 75% yield of the oxime was obtained, m.p. 82–84°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: N, 6.27. Found: N, 6.24.

1-(4'-Ethoxy-3'-methoxyphenyl)-isopropylamine.—A mixture of 190 g. (0.85 mole) of 1-(4'-ethoxy-3'-methoxyphenyl)-2-propanone oxime, 100 ml. of absolute alcohol, 50 ml. of liquid ammonia and 5 g. of Raney nickel catalyst was heated under 200 atmospheres of hydrogen with agitation. The reduction began at approximately 80° and was complete in one hour at final temperature of 120°. The catalyst was removed by filtration and the filtrate was fractionated to yield 169.5 g. (95%) of the amine, b.p. 162–165° (14 mm.), $n^{25}D$ 1.5259.

Anal. Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.60.

The following amines were prepared in the same manner:

1-(3',4'-Diethoxyphenyl)-isopropylamine.—The oxime was quickly reduced at 80°. The yield of amine was 88%, b.p. 154–157° (10 mm.), $n^{25}D$ 1.5151.

Anal. Calcd. for $C_{13}H_{21}NO_2$: N, 6.27. Found: N, 5.98.

1-(3'-Ethoxy-4'-methoxyphenyl)-isopropylamine.—B.p. 163–166° (15 mm.), yield 89%, $n^{25}D$ 1.5250.

Anal. Calcd. for $C_{12}H_{19}NO_2$: N, 6.69. Found: N, 6.79.

(11) During the course of the investigation this compound m.p. 59.5°, was reported as previously prepared *via* an alternate method by J. Kovács, *Acta Univ. Szegediensis, Sect. Sci. Nat. Acta Chem. Mineral. Phys.*, **1**, 109 (1943); *cf. C. A.*, **42**, 173c (1948).

(12) A. M. Eastham, H. E. Fisher, M. Kulka and H. Hibbert, THIS JOURNAL, **66**, 26 (1944).

(13) L. Balbiano and V. Paolini, *Gazz. chim. ital.*, **36**, I, 291 (1905).

1-(3′,4′-Dimethoxyphenyl)-isopropylamine.—B.p. 163–165° (18 mm.),[14] yield 83%, $n^{25}D$ 1.5328.

The amides of Table I, their intermediate acids, the isoquinolines of Table II and their salts, Table III, were prepared according to the methods described in the previous papers in this series.

6,7-Dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methylisoquinoline Phosphate.—A sample of this compound prepared in the usual manner utilizing an excess of phosphoric acid yielded a salt of m.p. 197–199° which analyzed unexpectedly high for phosphorus. The following more closely controlled conditions were found to be typical of a number of preparations:

Twenty grams (0.0545 mole) of 6,7-dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methylisoquinoline was dissolved in 200 ml. of hot 95% ethanol. Six and three-tenths grams (0.0545 mole) of 85% phosphoric acid was added rapidly with stirring. The salt precipitated readily. The crystalline suspension was chilled, filtered and rinsed with ethanol to yield 18.8 g. of the salt, m.p. 197–199°, unchanged on recrystallization from dilute alcohol. Calculated on the basis of phosphoric acid, this yield represented 98.7% of the theory in view of the analysis.

Anal. Dried at 100° for 3 hours *in vacuo* over phosphorus pentoxide. Calcd. for $C_{22}H_{25}NO_4 \cdot {}^1/_2H_3PO_4 \cdot {}^1/_2H_2O$: C, 50.48; H, 5.87; N, 2.68; P, 8.88. Found: C, 50.75; H, 5.91; N, 3.03; P, 8.88.

Concentration of the original mother liquor yielded a second crop of material weighing 5.8 g. It had a melting point of 121–122° which was not depressed when mixed with a sample of the original base. This therefore represented 86% of the unreacted base.

When the above procedure was repeated except that 10 g. (0.087 mole, or 1.6 moles of acid per mole of base) of phosphoric acid was employed, a salt identical with the above was obtained in 96.5% yield.

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(14) C. Mannich and W. Jacobsohn, *Ber.*, **43**, 189 (1910).

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY][1]

The Alkaline Isomerization of Humulone

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The isomerization of humulone (an antibiotic and flavoring component of hops) in alkaline methanol yields complex mixtures from which three crystalline isomers of humulone have been isolated in small yield. On the basis of evidence of chemical reactions and of absorption spectra, two of the compounds are best represented by structure II and the third by structure III. The three compounds are not bitter and are bacteriostatically inactive to several test organisms. In addition to the crystalline components, an oil is isolated consisting of at least two non-crystallizing components and a crystalline fraction. The two oily fractions are bacteriostatically inactive and intensely bitter. These structures have not been elucidated but they appear to be closely related to the crystalline isomers on the basis of chemical reactions and absorption spectra.

In connection with the investigation of antibiotic materials from hops related to humulone and lupulone, the alkaline rearrangement of humulone I[2] has been studied.

Verzele and Govaert[3] reported that refluxing a solution of humulone in absolute methanol containing sodium hydroxide yielded an oil which was named isohumulone. The material was considered interesting not only as a possible intermediate in the transformation of humulone (I) to humulinic acid (IV) or V,[4] but also as an important flavoring component or bitter principle of beer contributed by the humulone of hops.[5] Verzele and Govaert[3] proposed the structure II for the oil with the double bond of the chain attached to C_4 in the α,β-position rather than β,γ to the carbonyl group as shown. The product was characterized only by the equivalent weight, and the structure II was based on the evidence of equivalent weight, 362, the absorption of two moles of hydrogen catalytically to yield a tetrahydro derivative and degradation by aqueous alkali to yield humulinic acid and isobutyraldehyde.

Investigations in this Laboratory have shown that for rearrangement to occur in methanol, there must be an excess of alkali beyond that needed for the neutralization of the humulone. No reaction occurs when a methanolic solution of the sodium salt of humulone is refluxed for six hours. However, solutions of the sodium or potassium salt of humulone in methanol containing sodium hydroxide, potassium hydroxide, or sodium methylate in concentrations of 0.02–0.075 *N* when refluxed three to six hours yield oils in practically quantitative yields having equivalent weights from 370–380. That the humulone has been completely transformed is shown by the failure to yield an insoluble lead salt or *o*-phenylenediamine complex. From the oil, white crystalline material can be obtained in yields of 15–18%. Fractional crystallization from methanol separates the crude crystalline fraction into a less soluble levorotatory isomer and a more soluble dextrorotatory isomer. Fluorescent chromatography of the mother liquor yields a very

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) The structures for humulone and its degradation products are here written in the keto form rather than the enolic form. There is little reason to select the C_3-carbonyl of humulone as the enol, as is customary, in preference to the C_1-carbonyl, since either enol can form a hydrogen bridge with the keto group of R_2 to give a six-member ring. Cyclic 1,3-diones also form H-bonded dimers as well as intramolecular ones from infrared evidence (R. J. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949)).

(3) M. Verzele and F. Govaert, Int. Congress for Fermentation Industries, Lectures and Communications, Ghent, 297–301 (1947).

(4) Although the expression IV is ordinarily written for humulinic acid, the proof of structure of the compound (H. Wieland, *Ber.*, **58**, 102 (1925) and H. Wieland and E. Martz, *ibid.*, **59**, 2352 (1926)) did not eliminate the possibility of structure V. Both possible structures are here included as IV and V.

(5) W. Windisch, P. Kohlbach and R. Schleicher (*Woch. Brau.*, **44**, 453, 473, 485, 497 (1927)) observed that boiling aqueous solutions of humulone yielded resinous substances of greater bittering power than the original humulone.