chloride and extraction with ether of the hydantoin, left the peptide residue ready for the next cycle of treatment. A portion of the ether solution was spotted on paper for the identification of the thiohydantoin. The remainder of the solution was used for the hydrolysis in barium hydroxide solution[1] to the free amino acid for purposes of confirmation.

Chromatography.—Whatman #1 paper was found to be most suitable for the systems described. The large sheets were cut lengthwise into strips seven inches wide, which were buffered by dipping into a 0.05 *M* potassium acid phthalate–sodium hydroxide solution at *p*H 6. After the strips were dried in air, samples were applied to points three inches from one end of the paper and dried. Descending chromatography was employed.

Of the many solvent systems tried, the most satisfactory resolution was achieved with a mixture of xylene, glacial acetic acid and *p*H 6 phthalate buffer in a volume ratio of 3:2:1, respectively. The aqueous phase served as the equilibrating solvent while the organic phase was the developing solvent. After a 24-hour equilibration period, the chromatogram was allowed to develop to a length of 18 inches. At 25°, about three hours was required for development.

A second solvent system, 2-butanol–*p*H 6 phthalate buffer (7:1) was used primarily to identify the phenylthiohydantoins of arginine, aspartic acid, glutamic acid, histidine and cystine. This single phase system was used as both the equilibrating and developing solvent. After a short equilibration the chromatogram was allowed to develop for a period of four hours and attained a length of about eight inches. This length was quite satisfactory for the identification of the derivatives mentioned.

After the chromatograms had developed, the solvents were allowed to evaporate from the paper in a current of air until no trace of acetic acid or butanol remained. Grote's solution[7] was diluted with an equal volume of saturated sodium bicarbonate solution and applied to the chromatogram in the form of a spray. The phenylthiohydantoins appeared as red, blue or yellow spots after the paper was held over a steam-bath for several minutes. Since considerable fading occurred as the paper became dry, the location of each spot was marked while the paper was still damp. This procedure was facilitated by placing the chromatogram on a milk-glass plate, against which all spots were readily discernible.

Acknowledgment.—We are indebted to Dr. C. D. Bossinger for the preparation of some of the reference compounds utilized in this work.

(7) I. W. Grote, *J. Biol. Chem.*, **93**, 25 (1931). 0.5 g. of sodium nitroprusside, 0.5 g. of hydroxylamine hydrochloride and 1.0 g. of sodium bicarbonate are dissolved in 10 ml. of water. Two drops of bromine are added, the excess bromine removed by aeration, and the solution filtered and diluted to 25 ml. This stock solution is further diluted as specified for use.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

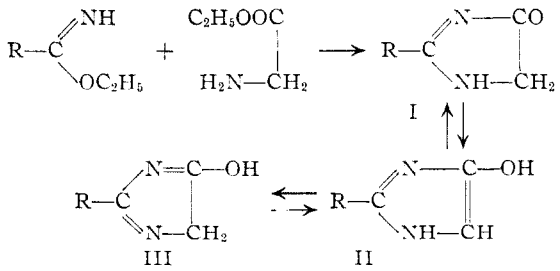
Derivatives of 4(5H)-Imidazolone

BY H. LEHR, S. KARLAN AND M. W. GOLDBERG

RECEIVED MARCH 12, 1953

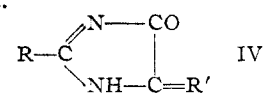
A series of new 4(5H)-imidazolone derivatives is described, obtained by the reaction of glycine ester with various imidic acid esters in the presence of a ketone. Some of the new compounds have shown hypnotic activity when tested in mice.

Only two imidazolones of the general formula I, with the oxygen atom in position 4, have so far been described, the 2-methyl-4(5H)-imidazolone (I, R = CH_3)[1] and the 2-benzyl-4(5H)-imidazolone (I, R = $C_6H_5CH_2$).[2] They were obtained by condensing glycine ester at room temperature with the ethyl esters of acetimidic or phenylacetimidic acid, respectively.[3]



These imidazolones are weak bases of limited stability and form stable hydrochlorides. Their reactions clearly indicate the existence of tautomerism. For example, the 2-benzyl-4(5H)-imidazolone gives a dibenzoyl derivative, probably derived from structure II, and a benzylidene derivative, which could be formed from I or III.[2]

The 4(5H)-imidazolones were of interest to us in connection with studies on new centrally active substances, and their synthesis was, therefore, reinvestigated. We were indeed able to obtain the two compounds described by Finger,[1,2] after modifying slightly his preparation method (cooling of the reaction mixture), but the yields were rather low, and it soon became apparent that the synthesis of new compounds of this series would require an improved method. In an attempt to find one, the condensation of glycine ester with various imidic acid esters was also carried out in the presence of solvents, such as benzene, dioxane and acetone. A new series of crystalline reaction products resulted when acetone was used. However, the new products were not the expected 4(5H)-imidazolones, but rather their 5-isopropylidene derivatives, formed from the imidazolones by a secondary condensation with acetone. Similar products were also obtained with many other aliphatic and hydroaromatic ketones, and also with ethyl acetoacetate, ethyl levulinate, acetophenone and 1-methyl-4-piperidone. Their structure is represented by the general formula IV, in which R can be an alkyl, aralkyl or aryl group (depending on the imidic acid ester used), and R′ is the radical introduced by the secondary condensation with a ketone.



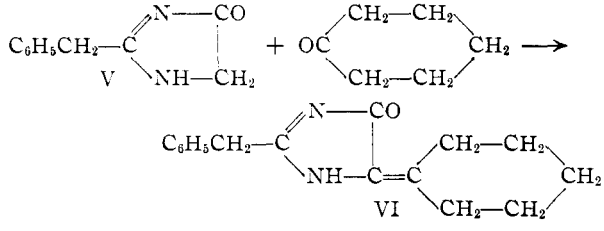
The structure of the new compounds was confirmed by synthesizing one of them, 2-benzyl-5-

(1) H. Finger, *J. prakt. Chem.*, [2] **76**, 93 (1907).

(2) H. Finger and W. Zeh, *ibid.*, [2] **82**, 50 (1910).

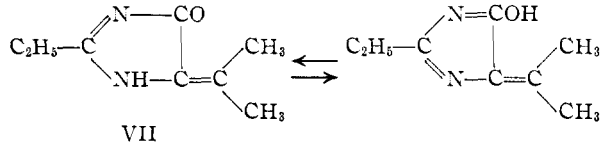
(3) Condensation at elevated temperatures leads to other products of not yet determined structure (Finger's isoglyoxalidones).

cyclohexylidene-4(5H)-imidazolone (VI), in two different ways: (1) by simultaneous reaction of phenylacetimidic acid ethyl ester, glycine ester and cyclohexanone, and (2) by condensation of preformed 2-benzyl-4(5H)-imidazolone (V) with cyclohexanone.



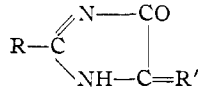
The new 4(5H)-imidazolone derivatives synthesized by us are listed in two tables.

Table I contains the compounds obtained with hydroaromatic ketones and Table II the products formed by condensation with aliphatic ketones, acetophenone and aliphatic keto esters. The free bases are colorless or slightly yellowish crystalline compounds which are more stable than the corresponding parent compounds with an unsubstituted CH_2-group in position 5. The latter, of course, must be formed as intermediates in our reactions. The compounds containing an aliphatic substituent in position 2 are actually not very stable at room temperature and must be stored in the refrigerator. However, they form stable, crystalline hydrochlorides. The compounds containing in position 2 an aryl or aralkyl radical are quite stable. In general, the free bases are soluble in the common organic solvents, and some of them, particularly those containing an aliphatic radical in position 2, are also soluble in water. All of them are soluble in strong acids and in strong alkali, probably because of the possibility of tautomerism, as also indicated by the differences in the ultraviolet absorption spectra of alkaline and acid solutions. Figure 1 illustrates this for 2-ethyl-5-isopropylidene-4(5H)-imidazolone (VII).



The new 4(5H)-imidazolone derivatives were tested in our Pharmacology Department under the

TABLE I



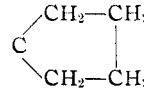
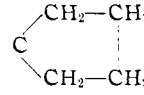
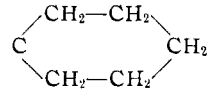
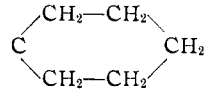
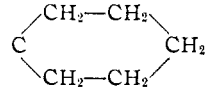
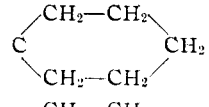
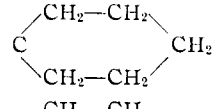
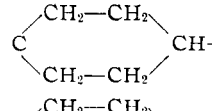
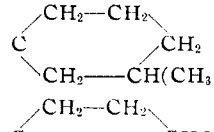
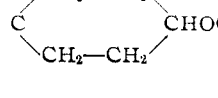
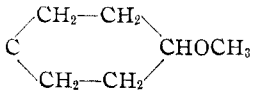
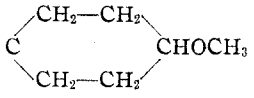
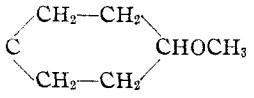
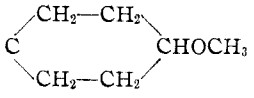
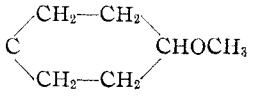
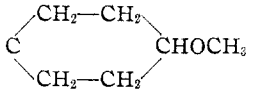
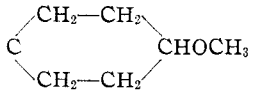
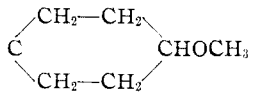
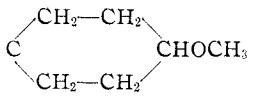
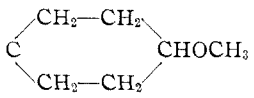
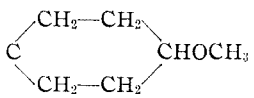
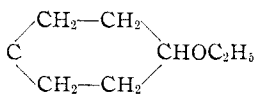
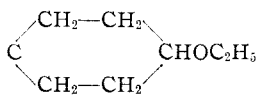
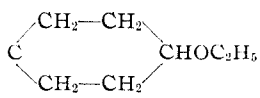
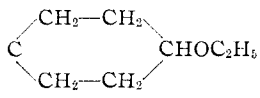
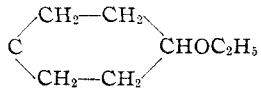
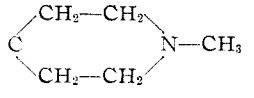
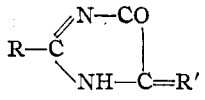
No.	R	R'	Type[a]	Formula	M.p., °C.[b]	Analyses, % Calcd.	Found
1	C_2H_5		B	$C_{10}H_{14}ON_2$	122–125	C, 67.38	67.49
						H, 7.92	8.17
2	$C_6H_5CH_2$		B	$C_{15}H_{16}ON_2$	180–191	C, 74.97	74.91
						H, 6.71	7.02
3	CH_3		B	$C_{10}H_{14}ON_2$	142–144	C, 67.40	67.78
						H, 7.92	7.95
4	C_2H_5		B	$C_{11}H_{16}ON_2$	142–143	C, 68.72	68.60
						H, 8.39	8.53
5	$CH_3OCH_2CH_2$		B	$C_{12}H_{18}O_2N_2$	125–127	C, 64.84	64.98
						H, 8.16	8.14
6	$C_6H_5CH_2$		B	$C_{16}H_{18}ON_2$	201–203	C, 75.56	75.02
						H, 7.13	6.92
7	C_6H_5		B	$C_{15}H_{16}ON_2$	198–200	C, 74.97	74.78
						H, 6.71	6.72
8	$CH_3CH_2CH_2$		B	$C_{13}H_{20}ON_2$	123–125	C, 70.87	70.45
						H, 9.15	8.75
9	$CH_3CH_2CH_2$		B	$C_{13}H_{20}ON_2$	133–135	C, 70.87	71.00
						H, 9.15	8.75
10	CH_3		B	$C_{11}H_{16}O_2N_2$	112–114	C, 63.44	63.37
						H, 7.75	7.66

TABLE I (*Continued*)

No.	R	R′	Type[a]	Formula	M.p., °C.[b]	Analyses, % Calcd.	Found
11	C_2H_5		B	$C_{12}H_{18}O_2N_2$	114–116	C, 64.84	64.86
						H, 8.16	8.06
11	C_2H_5		HCl	$C_{12}H_{18}O_2N_2 \cdot HCl$	190–192[c]	C, 55.70	55.30
						H, 7.40	7.56
12	$CH_3CH_2CH_2$		B	$C_{13}H_{20}O_2N_2$	115–116	C, 66.07	66.20
						H, 8.53	8.03
12	$CH_3CH_2CH_2$		HCl	$C_{13}H_{20}O_2N_2 \cdot HCl$	180–182[c]	C, 57.24	57.46
						H, 7.76	7.67
13	$CH_3CH_2CH_2CH_2$		B	$C_{14}H_{22}O_2N_2$	97–98	C, 67.16	67.49
						H, 8.86	8.40
13	$CH_3CH_2CH_2CH_2$		HCl	$C_{14}H_{22}O_2N_2$	168–170[c]	C, 58.62	58.77
						H, 8.08	8.32
14	$CH_3OCH_2CH_2$		B	$C_{13}H_{20}O_3N_2$	74–75	C, 61.88	61.89
						H, 7.99	7.67
15	$C_2H_5OCH_2CH_2$		B	$C_{14}H_{22}O_3N_2$	60–61	C, 63.13	63.07
						H, 8.33	8.27
16	$C_6H_5CH_2$		B	$C_{17}H_{20}O_2N_2$	167–169	C, 71.80	71.82
						H, 7.09	7.17
17	C_6H_5		B	$C_{16}H_{18}O_2N_2$	188–190	C, 71.08	71.52
						H, 6.71	6.49
18	p-$CH_3OC_6H_4$		B	$C_{17}H_{20}O_3N_2$	194–197	C, 67.98	68.00
						H, 6.71	6.87
19	CH_3		B	$C_{12}H_{18}O_2N_2$	130–132	C, 64.84	65.09
20	C_2H_5		B	$C_{13}H_{20}O_2N_2$	133–135	C, 66.07	65.72
						H, 8.53	8.31
20	C_2H_5		HCl	$C_{13}H_{20}O_2N_2 \cdot HCl$	199–201[c]	C, 57.24	57.58
						H, 7.76	7.69
21	$CH_3CH_2CH_2$		B	$C_{14}H_{22}O_2N_2$	116–117	C, 67.16	67.20
						H, 8.86	8.47
22	$CH_3CH_2CH_2CH_2$		B	$C_{15}H_{24}O_2N_2$	98–99	C, 68.14	68.04
						H, 9.15	8.71
23	C_2H_5		B	$C_{11}H_{17}ON_3$	162–164[c]	C, 63.74	64.06
						H, 8.27	8.35

[a] B, base; HCl, hydrochloride. [b] All melting points are corrected. [c] With decomposition.

TABLE II



No.	R	R′	Type[a]	Formula	M.p., °C.[b]	Analyses, % Calcd.	Found
24	CH_3	$C(CH_3)_2$	B	$C_7H_{10}ON_2$	142–144	C, 60.85	60.77
						H, 7.30	7.47
25	C_2H_5	$C(CH_3)_2$	B	$C_8H_{12}ON_2$	111–112	C, 63.13	63.08
						H, 7.95	7.94
26	$CH_3CH_2CH_2$	$C(CH_3)_2$	B	$C_9H_{14}ON_2$	110–111	C, 65.03	65.02
						H, 8.49	8.36
27	$CH_3CH_2CH_2CH_2$	$C(CH_3)_2$	HCl	$C_{10}H_{16}ON_2 \cdot HCl$	217–219[c]	C, 55.42	55.76
						H, 7.91	7.61
28	$C_6H_5CH_2$	$C(CH_3)_2$	B	$C_{13}H_{14}ON_2$	165–166	C, 72.87	73.16
						H, 6.59	6.83
29	C_6H_5	$C(CH_3)_2$	B	$C_{12}H_{12}ON_2$	200–201	C, 71.98	71.69
						H, 6.04	6.12
30	p-$O_2NC_6H_4CH_2$	$C(CH_3)_2$	B	$C_{13}H_{13}O_3N_3$	211–212	C, 60.22	60.46
						H, 5.05	4.92
31	p-$O_2NC_6H_4$	$C(CH_3)_2$	B	$C_{12}H_{11}O_3N_3$	258–260	C, 58.77	59.03
						H, 4.52	4.87
32	$CH_3CH_2CH_2$	$C(CH_3)(C_2H_5)$	B	$C_{10}H_{16}ON_2$	106–108	C, 66.63	66.59
						H, 8.95	8.99
33	$CH_3CH_2CH_2$	$C(CH_3)(C_3H_7\text{-}n)$	HCl	$C_{11}H_{18}ON_2 \cdot HCl$	159–161[c]	C, 57.25	57.47
						H, 8.30	8.19
34	$C_6H_5CH_2$	$C(CH_3)(C_3H_7\text{-}n)$	B	$C_{15}H_{18}ON_2$	88–90	C, 74.35	74.41
						H, 7.49	7.29
35	p-$CH_3O—C_6H_4$	$C(CH_3)(C_3H_7\text{-}n)$	B	$C_{15}H_{18}O_2N_2$	175–177	C, 69.74	69.98
						H, 7.02	6.81
36	$CH_3CH_2CH_2$	$C(CH_3)(C_3H_7\text{-}iso)$	HCl	$C_{11}H_{18}ON_2 \cdot HCl$	181–183[c]	C, 57.25	57.08
						H, 8.30	8.14
37	$CH_3CH_2CH_2$	$C(CH_3)(C_4H_9\text{-}iso)$	HCl	$C_{12}H_{20}ON_2 \cdot HCl$	198–200[c]	C, 58.88	58.72
						H, 8.65	8.37
38	$CH_3CH_2CH_2$	$C(CH_3)(C_5H_{11}\text{-}n)$	HCl	$C_{13}H_{22}ON_2 \cdot HCl$	157–159[c]	C, 60.33	60.36
						H, 8.96	8.71
39	$CH_3CH_2CH_2$	$C(CH_3)(C_6H_{13}\text{-}n)$	HCl	$C_{14}H_{24}ON_2 \cdot HCl$	158–160[c]	C, 61.63	61.80
						H, 9.24	8.94
40	$CH_3CH_2CH_2$	$C(CH_3)(C_9H_{19}\text{-}n)$	HCl	$C_{17}H_{30}ON_2 \cdot HCl$	153–156[c]	C, 64.84	64.83
						H, 9.92	9.77

TABLE II (*Continued*)

No.	R	R′	Type[a]	Formula	M.p., °C.[b]	Analyses, % Calcd.	Found
41	$CH_3CH_2CH_2$	$C(CH_3)(CH_2CH_2CH{=}CH_2)$	HCl	$C_{12}H_{18}ON_2\cdot HCl$	155–157[c]	C, 59.37 H, 7.89	59.59 7.74
42	$CH_3CH_2CH_2$	$C(CH_3)[(CH_2)_3N(C_2H_5)_2]$	HCl[d]	$C_{15}H_{27}ON_3\cdot 2HCl$	207–208	C, 53.25 H, 8.64	52.77 8.69
43	$CH_3CH_2CH_2$	$C(CH_3)(CH_2C_6H_5)$	B	$C_{15}H_{18}ON_2$	131–132	C, 74.35 H, 7.49	74.39 7.39
44	$CH_3CH_2CH_2$	$C(CH_3)(C_6H_5)$	B	$C_{14}H_{16}ON_2$	115–117	C, 73.65 H, 7.07	73.51 6.97
44	$CH_3CH_2CH_2$	$C(CH_3)(C_6H_5)$	HCl	$C_{14}H_{16}ON_2\cdot HCl$	204–205[c]	C, 63.50 H, 6.47	63.21 6.19
45	$CH_3CH_2CH_2$	$C(CH_3)(CH_2{-}COOC_2H_5)$	B	$C_{12}H_{18}O_3N_2$	120–122	C, 60.48 H, 7.61	60.79 7.36
46	$CH_3CH_2CH_2$	$C(CH_3)[(CH_2)_2{-}COOC_2H_5]$	HCl	$C_{13}H_{20}O_3N_2\cdot HCl$	164–166[c]	C, 54.07 H, 7.33	54.21 7.47
47	$CH_3CH_2CH_2$	$C(C_2H_5)_2$	HCl	$C_{11}H_{18}ON_2\cdot HCl$	178–180[c]	C, 57.25 H, 8.30	57.66 8.49
48	$CH_3CH_2CH_2$	$C(CH_2{-}C_6H_5)_2$	HCl	$C_{21}H_{22}ON_2\cdot HCl$	216–219	C, 71.07 H, 6.53	71.22 6.72

[a] B, base; HCl, hydrochloride. [b] All melting points are corrected. [c] With decomposition. [d] Dihydrochloride.

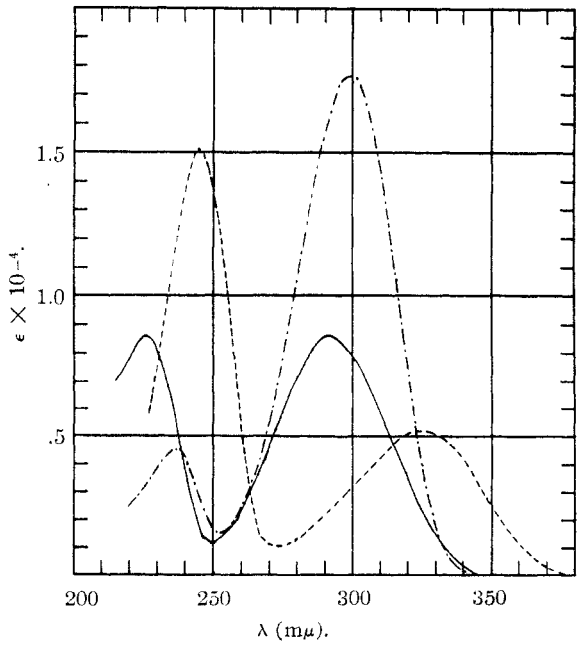


Fig. 1.—Ultraviolet absorption spectrum of 2-ethyl-5-isopropylidene-4(5H)-imidazolone: - - - -, in 1 *N* KOH; ·····, in 100% H_2SO_4; —, in *p*H 7 phosphate buffer (same in petroleum ether and in isopropyl alcohol).

direction of Dr. W. M. Benson. A number of them produced hypnosis in mice when given intraperitoneally. The more interesting compounds are recorded in Table III, which also lists their 50% hypnotic dose (HD_{50}) and 50% lethal dose (LD_{50}). The most active product was the hydrochloride of 2-propyl-5-(1-methylhexylidene)-4(5H)-imidazolone (No. 38, HD_{50} = 109 mg./kg., LD_{50} = 469 mg./kg.). However, none of the compounds tested has shown an appreciable activity upon oral administration.

TABLE III

Compound No.	Type[a]	Mg./kg. in mice (i.p.) HD_{50}	LD_{50}	Compound No.	Type[a]	Mg./kg. in mice (i.p.) HD_{50}	LD_{50}
4	B	400	640	28	B	300	460
11	B	413	1220	36	HCl	229	463
11	HCl	422	1312	37	HCl	129	434
12	B	207	818	38	HCl	109	469
12	HCl	200	965	39	HCl	238	650
13	HCl	137	458	41	HCl	159	536
26	B	575	850	44	HCl	175	632
27	HCl	418	800				

[a] B, base; HCl, hydrochloride.

Experimental

Starting Materials.—*The imidic acid esters* used in this study were obtained from the corresponding nitriles by reaction with an equimolecular amount of absolute ethanol and

dry hydrogen chloride at 0°. In most instances the hydrochlorides crystallized out. In some cases, it was necessary to add ether to induce crystallization. The free imidic acid esters were prepared by adding an excess of 40% NaOH to the solution of the hydrochlorides in a minimum amount of water, saturating with potassium carbonate and extracting with ether. The dried extracts yielded the free imidic acid esters as colorless liquids which were used for the condensation reactions without further purification. Of the imidic acid esters thus prepared, two, namely, β-methoxypropionimidic acid ethyl ester and β-ethoxypropionimidic acid ethyl ester, had not yet been described. Their hydrochlorides were rather hygroscopic and unstable, and had to be converted immediately into the desired 4(5H)-imidazolone derivatives. *p*-Nitrophenylacetimidic acid ethyl ester hydrochloride is mentioned in the literature.[4] The corresponding free imidic ester was obtained by us in crystalline form, m.p. 57–59°, from acetone–water.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81. Found: C, 57.67; H, 5.44.

The ketones employed were, with one exception, known compounds.

***p*-Ethoxycyclohexanone**, a new compound, was prepared as follows: Thirty-four and one-half grams of hydroquinone monoethyl ether, dissolved in 200 cc. of absolute ethanol, was hydrogenated in the presence of Raney nickel at 200° and 2000 lb. pressure. After 3 hours the solution was filtered and the solvent removed *in vacuo*. The residue was fractionated, yielding 30 g. (83%) of *p*-ethoxycyclohexanol, distilling at 106–107° (13 mm.) as a colorless liquid.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.75; H, 11.06.

One hundred and ten grams of *p*-ethoxycyclohexanol was added, with stirring, to a solution of 200 g. of potassium dichromate in 825 cc. of water and 250 g. of concd. H_2SO_4 at 0°. The temperature rose to about 80–90°. After having reached room temperature, the mixture was extracted six times with 200-cc. portions of ether. The combined extracts were dried over anhydrous sodium sulfate and the ether distilled off. The residue was fractionated *in vacuo*, yielding 59 g. (55%) of *p*-ethoxycyclohexanone; colorless liquid boiling at 88–90° (12 mm.). The semicarbazone melted at 186–188°.

Anal. Calcd. for $C_9H_{17}O_2N_3$: N, 21.09. Found: N, 21.40.

4(5H)-Imidazolone Derivatives.—These compounds were prepared by refluxing for 5–22 hours equimolecular amounts of an imidic acid ester, glycine ethyl ester and a ketone in benzene or in an excess of the ketone as solvent. In some instances, usually in the case of the 2-aryl or 2-aralkyl compounds, the end product crystallized from the hot reaction mixture or after cooling. In most of the cases, the solvent had to be removed *in vacuo*, and the residue, a solid containing various amounts of oily by-products, was then purified by crystallization from ligroin, benzene or acetone, or a mixture of these solvents. In the case of the 2-alkyl derivatives, condensed in position 5 with a higher aliphatic ketone, the residues obtained after removal of the solvent were viscous oils which did not solidify. These oils were extracted with low boiling ligroin, and the extracts were evaporated to dryness. The residues thus obtained were light-colored liquids which were directly converted to the corresponding crystalline hydrochlorides.

The hydrochlorides were obtained by dissolving the base in a minimum amount of absolute ethanol and saturating the cooled solution with dry hydrogen chloride. Careful addition of absolute ether induced crystallization of the hydrochlorides, which was completed by allowing the mixture to stand in the refrigerator. In almost all instances, concentration of the mother liquors yielded additional amounts of crystals.

(4) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 400 (1930).

The following three preparations are representative examples of the methods used for the synthesis of the compounds listed in Tables I and II: (a) use of an excess of the ketone as solvent, (b) use of benzene as solvent, (c) isolation in form of the hydrochloride.

(a) The 2-Benzyl-5-isopropylidene-4(5H)-imidazolone.—Phenylacetimidic acid ethyl ester (16 g.) and glycine ethyl ester (10 g.) were refluxed for 7 hours in 50 cc. of acetone. The reaction mixture was then kept for 2 days at room temperature. The precipitated product was filtered off and dried. Concentration of the mother liquor *in vacuo* gave two additional crops of crystals which were combined with the main crop. Recrystallization from benzene yielded 10 g. (47.5%) of 2-benzyl-5-isopropylidene-4(5H)-imidazolone in form of white needles; m.p. 165–166°. Compounds no. 24–31, 33, 34, 35, 46 and 47 were prepared by this method.

(b) The 2-*n*-Propyl-5-(*p*-methoxycyclohexylidene)-4(5H)-imidazolone.—Butyrimidic acid ethyl ester (47 g.), glycine ethyl ester (42 g.) and *p*-methoxycyclohexanone (50 g.) were refluxed for 6 hours in 200 cc. of benzene. After standing overnight at room temperature, the solution was evaporated to dryness *in vacuo*. The crystalline residue, containing some oily by-products, was recrystallized from ligroin (b.p. 60–90°). Forty-five grams (48%) of 2-*n*-propyl-5-(*p*-methoxycyclohexylidene)-4(5H)-imidazolone was thus obtained as white needles melting at 115–116°. Compounds no. 1–23, 32, 43 and 44 were prepared by this method.

(c) 2-*n*-Propyl-5-(α-methylisobutylidene)-4(5H)-imidazolone Hydrochloride.—Butyrimidic acid ethyl ester (34 g.), glycine ethyl ester (30 g.) and methyl isopropyl ketone (50 cc.) were mixed and the mixture refluxed for 6 hours. After cooling, the solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. The brown viscous residue was dissolved in 200 cc. of acetone, the solution was filtered and evaporated to dryness. The oily residue was extracted 3 times with 200-cc. portions of ligroin (b.p. 60–90°). The combined extracts were treated with a small amount of activated carbon and evaporated to dryness *in vacuo*. The light colored oil thus obtained was dissolved in 25 cc. of absolute ethanol, the solution was cooled with ice-water and saturated with dry hydrogen chloride. After careful addition of absolute ether until beginning turbidity, the solution was kept for 15 hours in the refrigerator. The white crystals of 2-*n*-propyl-5-(α-methylisobutylidene)-4(5H)-imidazolone hydrochloride were filtered off and washed with alcohol–ether (1:3). Concentration of the mother liquors *in vacuo* yielded an additional crop of crystals which was combined with the main fraction. Recrystallization from ethanol–ether gave a product melting at 181–183° with decomposition; yield 16 g. (24%). Compounds no. 36–42, 46 and 48 were prepared by this method.

Condensation of 2-Benzyl-4(5H)-imidazolone with Cyclohexanone.—One gram of 2-benzyl-4(5H)-imidazolone[2] was dissolved in 5 cc. of cyclohexanone with slight warming. The solution was kept for about 30 minutes in a boiling water-bath. The precipitated crystals were filtered off and recrystallized from 70% ethanol; m.p. 202–203°. The mixed melting point with a sample of 2-benzyl-5-cyclohexylidene-4(5H)-imidazolone obtained by simultaneous condensation of phenylacetimidic acid ethyl ester, glycine ethyl ester and cyclohexanone showed no depression. When the condensation of 2-benzyl-4(5H)-imidazolone with cyclohexanone was carried out in the presence of piperidine as catalyst, the end product crystallized within 5 minutes.

Acknowledgments.—Our thanks are due to Dr. W. M. Benson, Dr. L. O. Randall and their staff for the pharmacological data, to Dr. A. Steyermark and his staff for the microanalyses, to Dr. A. Motchane for the absorption spectra and to Mr. V. McKenna for assistance in the preparation of some of the compounds.

NUTLEY, N. J.