an index value of 1. No attempt has been made to relate these figures with the partition coefficients since there is no obvious reason why lipoid solubility should be related to effects of this kind.

The toxicity of the compounds was determined on cats and on the seedlings of lupinus albus. No relationship was expected in these figures, since such an effect as toxicity could hardly be predicted from any one set of physical properties; hence they are not included in this paper.

Discussion

It is felt that from the preceding data it may be stated that there has been demonstrated herein a definite relationship between physical and physiological properties of hydroxybenzyl alcohols. It is interesting to note how the actions of the mono-alkyl and mono-halogen derivatives are related according to their partition coefficients without regard to the great difference in chemical nature of the substituent groups, as may be seen in Fig. 1.

The question of the position of the substituent group in the parent molecule has also been considered in the case of the three isomeric methyl saligenins. It is seen that the bactericidal power depends more on the physical properties of the molecule than on the position of the inert group.

As mentioned previously, shifting the relative positions of the functioning group changes the nature of the molecule, so that there can be no comparison between saligenin and its analogs. It is to be noted, however, that in comparing each analog to its respective derivatives, the relation of physical to physiological properties holds good.

Summary

The partition coefficients between oil and water of a series of derivatives, analogs and homologs, of saligenin (*o*-hydroxybenzyl alcohol) have been determined and compared with the bacteriological and pharmacological properties of the compounds. A definite relationship exists, even in cases where the structures of the inert substituent groups differ greatly.

BALTIMORE, MARYLAND RECEIVED JUNE 4, 1936

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

Studies in the Phenanthrene Series. XI. Propanolamines of the Type $C_{14}H_9CHOHCH_2CH_2NR_2$[1]

BY JACOB VAN DE KAMP AND ERICH MOSETTIG

The pharmacological study of a number of amino alcohols in the phenanthrene series[2] has shown that some of these compounds, carrying the side chain $-CHOHCH_2NR_2$ (type I)[3] and $-CHOHCH(CH_3)NR_2$ (type II),[4] exhibit a decided analgesic action. In both types of compounds the nitrogen atom is located in the side chain in the β-position to the phenanthrene nucleus. Through the systematic investigations by Barger and Dale and associates[5] of the amines $Ar(CH_2)_xNH_2$ (Ar being the phenyl, hydroxyphenyl or iminazolyl group), it became evident that almost universally the greatest physiological action (in particular with respect to blood pressure) is exerted by the compounds in which $x = 2$. As Barger points out, compounds of this type occur frequently in nature and are probably in some instances intermediates in the phytosynthesis of isoquinoline derivatives. In the compounds with $x < 2$ or $x > 2$, the physiological action is greatly diminished. It was of interest to determine, by comparison of the phenanthrene alkamines of type I and II[6] on the one hand with the compounds of the type $C_{14}H_9CHOHCH_2CH_2NR_2$ on the other, whether or not a similar regularity may be observed with the phenanthrene derivatives of these series, particularly in respect to their analgesic action.

The propanolamines described in this communication were prepared essentially by the Mannich method,[7] starting from 2-, 3- and 9-acetylphenanthrenes: $C_{14}H_9COCH_3 + CH_2O + HNR_2$.

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) Eddy, *J. Pharmacol.*, **55**, 419 (1935).

(3) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933).

(4) Mosettig and Czerwin, unpublished results.

(5) Barger, "Some Applications of Organic Chemistry to Biology and Medicine," McGraw-Hill Book Co., Inc., New York City, 1930, pp. 73–100.

(6) The comparison of type I and type II has shown that the compounds of type II are generally slightly weaker analgesics than those of type I.[2]

(7) Mannich, *Arch. Pharm.*, **255**, 261 (1917); Mannich and Braun, *Ber.*, **53**, 1874 (1920); Mannich and Heilner, *ibid.*, **55**, 356 (1922); Mannich and Lammering, *ibid.*, **55**, 3510 (1922).

TABLE I

COMPOUNDS, PROPERTIES AND ANALYSES

Phenanthrene derivatives	Solvent	Appearance	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-(3-(Dimethylamino)-1-oxo-propyl)-	Et_2O	Colorless plates	104.5–105	$C_{19}H_{19}ON$	82.26	82.70	6.91	6.95
Hydrochloride	EtOH-Et_2O	Colorless plates	193 –193.5	$C_{19}H_{20}ONCl$			Cl, 11.31	11.48
Perchlorate	EtOH	Colorless plates	167 –167.5	$C_{19}H_{20}O_5NCl$			N, 3.71	3.85
3-(3-(Dimethylamino)-1-oxo-propyl)-·HCl	EtOH-Et_2O	Colorless needles	177.5–178	$C_{19}H_{20}ONCl$			Cl, 11.31	11.02
Picrate	EtOH	Yellow needles	175.5–176	$C_{25}H_{22}O_8N_4$			N, 11.07	11.30
9-(3-(Dimethylamino)-1-oxo-propyl)-·HCl	EtOH-Et_2O	Colorless leaflets	171 –171.5	$C_{19}H_{20}ONCl$			Cl, 11.31	11.46
Picrate	EtOH	Yellow blades	175 –175.5	$C_{25}H_{22}O_8N_4$			N, 11.07	11.08
2-(3-Diethylamino)-1-oxo-propyl-·HCl	EtOH	Colorless plates	167 –167.5	$C_{21}H_{24}ONCl$			Cl, 10.38	10.49
3-(3-(Diethylamino)-1-oxo-propyl)-·HCl	EtOH-Et_2O	Colorless blades	155.5–156	$C_{21}H_{24}ONCl$			Cl, 10.38	10.35
Picrate	EtOH	Yellow prisms	108 –109	$C_{27}H_{26}O_8N_4$			N, 10.49	10.48
9-(3-(Diethylamino)-1-oxo-propyl)-·HCl	EtOH-Et_2O	Colorless leaflets	135 –136	$C_{21}H_{24}ONCl$			Cl, 10.38	10.35
Salicylate	EtOH-Et_2O	Colorless prisms	113 –113.5	$C_{28}H_{29}O_4N$			N, 3.16	3.31
2-(3-(Piperidino)-1-oxo-propyl)-	Et_2O-pet. ether	Colorless plates	88.5– 89	$C_{22}H_{23}ON$			N, 4.42	4.50
Hydrochloride	H_2O	Colorless plates	220 –220.5	$C_{22}H_{24}ONCl$			Cl, 10.03	9.78
3-(3-(Piperidino)-1-oxo-propyl)-·HCl	H_2O	Colorless plates	201 –201.5	$C_{22}H_{24}ONCl$			Cl, 10.03	10.29
Picrate	EtOH	Yellow leaflets	162.5–163.5	$C_{28}H_{26}O_8N_4$			N, 10.26	10.35
9-(3-(Piperidino)-1-oxo-propyl)-·HCl	EtOH-Et_2O	Colorless prisms	184 –185	$C_{22}H_{24}ONCl$			Cl, 10.03	10.21
Picrate	EtOH	Yellow plates	138 –139	$C_{28}H_{26}O_8N_4$			N, 10.26	10.43
2-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-oxo-propyl)-	EtOH	Colorless leaflets	133.5–134	$C_{26}H_{23}ON$	85.44	85.50	6.35	6.14
Hydrochloride	EtOH	Colorless prisms	208 –209	$C_{26}H_{24}ONCl$			Cl, 8.83	9.28
3-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-oxo-propyl)-	$CHCl_3$-Et_2O	Colorless prisms	118.5–119	$C_{26}H_{23}ON$	85.44	85.23	6.35	6.60
Hydrochloride	EtOH	Colorless needles	219 –220	$C_{26}H_{24}ONCl$			Cl, 8.83	9.01
9-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-oxo-propyl)-·HCl	EtOH	Colorless needles	228.5–229	$C_{26}H_{24}ONCl$	77.68	77.72	6.02	6.38
2-(3-(Dimethylamino)-1-hydroxy-*n*-propyl)-	[a]	Colorless plates	97.5– 98	$C_{19}H_{21}ON$	81.67	81.61	7.58	7.87
Picrate	EtOH	Yellow blades	156 –157	$C_{25}H_{24}O_8N_4$			N, 11.03	10.96
2-(3-(Dimethylamino)-1-benzoxy-*n*								
propyl)-·HCl	EtOH-Et_2O	Colorless needles	219 –219.5	$C_{26}H_{26}O_2NCl$			Cl, 8.45	8.26
3-(3-(Dimethylamino)-1-hydroxy-*n*-propyl)-	[a]	Colorless needles	99 –100	$C_{19}H_{21}ON$	81.67	81.84	7.58	7.81
9-(3-(Dimethylamino)-1-hydroxy-*n*-propyl)-	[b]	Colorless oil		$C_{19}H_{21}ON$	81.67	81.91	7.58	7.74
Perchlorate	EtOH-Et_2O	Colorless plates	142.5–143	$C_{19}H_{22}O_5NCl$			N, 3.69	3.67
Picrate	EtOH	Yellow prisms	167.5–168	$C_{25}H_{24}O_8N_4$			N, 11.03	11.07
2-(3-(Diethylamino)-1-hydroxy-*n*-propyl)-	[a]	Colorless prisms	91 – 92	$C_{21}H_{25}ON$	82.03	82.45	8.20	8.24
2-(3-(Diethylamino)-1-benzoxy-*n*-								
propyl)-·HCl	EtOH-Et_2O	Colorless prisms	166 –167	$C_{28}H_{29}O_2NCl$			Cl, 7.92	8.05
3-(3-(Diethylamino)-1-hydroxy-*n*-propyl)-	[a]	Colorless liquid		$C_{21}H_{25}ON$	82.03	81.74	8.20	8.25
Hydrochloride	EtOH-Et_2O	Colorless prisms	141 –143	$C_{21}H_{26}ONCl$			N, 4.08	3.95
9-(3-(Diethylamino)-1-hydroxy-*n*-propyl)-	[a]	Colorless oil		$C_{21}H_{25}ON$	82.03	82.21	8.20	7.82
2-(3-(Piperidino)-1-hydroxy-*n*-propyl)-	[b]	Colorless rods	128 –128.5	$C_{22}H_{25}ON$	82.71	82.47	7.89	7.49
Hydrochloride	EtOH	Colorless prisms	184 –185	$C_{22}H_{26}ONCl$			Cl, 9.97	9.81
3-(3-(Piperidino)-1-hydroxy-*n*-propyl)-	[b]	Colorless liquid		$C_{22}H_{25}ON$	82.71	82.73	7.89	7.50
Hydrochloride	EtOH-Et_2O	Colorless plates	185 –185.5	$C_{22}H_{26}ONCl$	N, 3.94	3.76	Cl, 9.97	9.85
3-(3-(Piperidino)-1-acetoxy-*n*-propyl)-·HCl	EtOH-Et_2O	Colorless leaflets	237.5–238	$C_{24}H_{25}O_2NCl$			Cl, 8.92	8.94
9-(3-(Piperidino)-1-hydroxy-*n*-propyl)-	[c]	Colorless prisms	126 –126.5	$C_{22}H_{25}ON$	82.71	82.62	7.89	8.12
Picrate	EtOH	Yellow prisms	193.5–194	$C_{28}H_{28}O_8N_4$			N, 10.22	10.19
2-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-hydroxy-*n*-propyl)-	EtOH	Colorless prisms	132.5–133	$C_{26}H_{25}ON$	84.97	84.83	6.86	7.10
Hydrochloride	EtOH-Et_2O	Colorless plates	212.5–213	$C_{26}H_{26}ONCl$			Cl, 8.78	8.79
3-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-hydroxy-*n*-propyl)-	EtOH	Colorless plates	117 –117.5	$C_{26}H_{25}ON$	84.97	85.04	6.86	7.15
Hydrochloride	EtOH	Colorless plates	208 –208.5	$C_{26}H_{26}ONCl$	77.29	77.51	6.49	6.72
							N, 3.47	3.60
9-(3-(1,2,3,4-Tetrahydroisoquinolino)-								
1-hydroxy-*n*-propyl)-		Colorless oil	[b]	$C_{26}H_{25}ON$	84.97	84.90	6.86	6.99

[a] Distilled at 100° (0.01 mm.). [b] Distilled at 130° (0.01 mm.). [c] Sublimed at 100° (0.01 mm.).

$HCl \longrightarrow C_{14}H_9COCH_2CH_2NR_2 \cdot HCl \xrightarrow{\text{cat. red.}} C_{14}H_9CHOHCH_2CH_2NR_2 \cdot HCl$, where $-NR_2$ represents the dimethylamino-, diethylamino-, piperidino- and tetrahydroisoquinolino group.

We wish to express our gratitude to Merck and Co., Rahway, N. J., for their generous coöperation in the large scale preparation of the 2- and 3-acetylphenanthrenes.

Experimental

A mixture of 2-, 3-[8] or 9-acetylphenanthrene[9] (0.1 mole), paraformaldehyde (0.15 mole), and the secondary amine hydrochloride (0.15 mole) (dimethylamine-, diethylamine, piperidine- and 1,2,3,4-tetrahydroisoquinoline hydrochloride) in 60 to 80 cc. of isoamyl alcohol was kept at a gentle boil for five to twenty minutes. The advantage of using the higher boiling solvent, isoamyl alcohol, in this

(8) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).
(9) Mosettig and van de Kamp, *ibid.*, **55**, 3442 (1933).

condensation is that the reaction proceeds much quicker, whereas in ethyl alcohol, the solvent used by Mannich, the condensation takes place very slowly. By prolonged boiling in ethyl alcohol, furthermore, the yield of the expected amino ketone is considerably lowered, on account of the formation of by-products. These are both neutral and basic in nature and in part crystalline. In the preparation of most of the piperidino and tetrahydroisoquinolino ketones the hydrochlorides crystallized out after five to ten minutes. They were filtered off from the cooled reaction mixture and recrystallized. In the cases where the hydrochlorides did not precipitate, the reaction mixture was cooled, after having been kept boiling for fifteen to twenty minutes. After the addition of a few drops of concentrated hydrochloric acid, in order to depolymerize unchanged paraformaldehyde, unreacted ketone and formaldehyde were taken up in ether. The aqueous layer was alkalified and extracted with ether and the residue left from evaporation of the ether was warmed slightly in a vacuum in order to remove aliphatic amines. The amino ketones subsequently were purified through the hydrochlorides.

The amino ketones were reduced in the form of the hydrochlorides, in 50–70% ethyl alcohol, using platinum oxide as a catalyst. In two cases where the free amino ketones were reduced, namely, in the cases of the 3-dimethylamino ketone and the 9-(1,2,3,4-tetrahydroisoquinolino) ketone, two moles of hydrogen were absorbed, and in the case of the 2-dimethylamino ketone, approximately three moles of hydrogen were taken up. The reduction of the 3-(1,2,3,4-tetrahydroisoquinolino) ketone was effected with good results either by hydrogenating the free base in 95% ethyl alcohol, or by reducing the hydrochloride in 60% ethyl alcohol.

Summary

1. A series of amino ketones of the type $C_{14}H_9COCH_2CH_2NR_2$ (NR_2 representing the dimethylamino-, the diethylamino-, the piperidino- and tetrahydroisoquinolino group) has been prepared by the Mannich method from 2-, 3- and 9-acetylphenanthrene.

2. By catalytic hydrogenation the corresponding amino alcohols $C_{14}H_9CHOHCH_2CH_2NR_2$ have been prepared. These substances will be investigated to determine the result pharmacologically of lengthening the carbon chain of amino alcohols of the phenanthrene series.

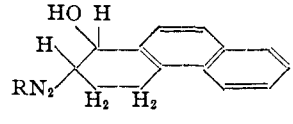
UNIVERSITY, VIRGINIA RECEIVED JUNE 22, 1936

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

Studies in the Phenanthrene Series. XII.[1] Amino Alcohols Derived from 1,2,3,4-Tetrahydrophenanthrene[2]

BY ALFRED BURGER AND ERICH MOSETTIG

Among the synthetical substances which have been prepared in this Institution in the attempt to find morphine substitutes, 2-piperidino-1-hydroxy-1,2,3,4-tetrahydrophenanthrene (type I), and 3-(1,2,3,4-tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene (type II) proved to have the strongest analgesic action (minimal effective doses administered orally to cats, 20 and 15 mg. per kilogram, respectively, comparable with doses of 20 mg. for pseudocodeine, 10 mg. for codeine, and 1 mg. for morphine).[2] Experiments are under way to resolve these compounds and eliminate or "muzzle" their alcoholic hydroxyl in the hope of increasing their physiological activity.[3]



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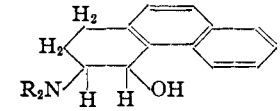
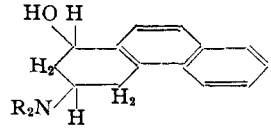
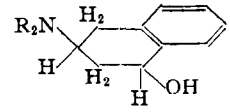


II

We are reporting in the present communication the preparation of compounds which differ from those of types I and II principally through the position of the nitrogen group. Compounds which may be represented by type formulas III and IV, analogs of the propanolamines reported in the foregoing communication, are obviously not readily accessible.



III



IV

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) First communication on amino alcohols derived from 1,2,3,4-tetrahydrophenanthrene, Mosettig and Burger, THIS JOURNAL, **57**, 2189 (1935).

(3) Elimination and muzzling of the alcoholic group in morphine and its derivatives produce generally a marked increase in analgesic action. Eddy, *J. Pharmacol.*, **55**, 127 (1935); Eddy and Howes, *ibid.*, **55**, 257 (1935).