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N-Substituted Epoxymorphinans

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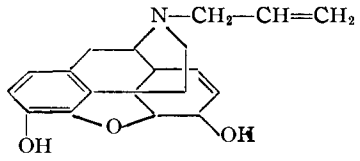
A number of N-substituted derivatives of normorphine has been prepared and tested for morphine antagonizing activity. Others have been prepared from related epoxymorphinans including the dihydro-, desoxy- and dihydrodesoxynormorphine series plus various dihydronormorphinones. Pharmacological activity of these compounds can be summarized by the statement that substitution of allyl, *n*-propyl, methallyl or isobutyl for methyl in all series produced compounds capable of counteracting the analgesic effect of morphine. Several other analgesics were converted to N-allyl derivatives but these compounds were not morphine antagonists.

The extraordinary effectiveness of N-allylnormorphine (I, Nalline[R]) in counteracting the respiratory depressant and analgesic properties of mor-

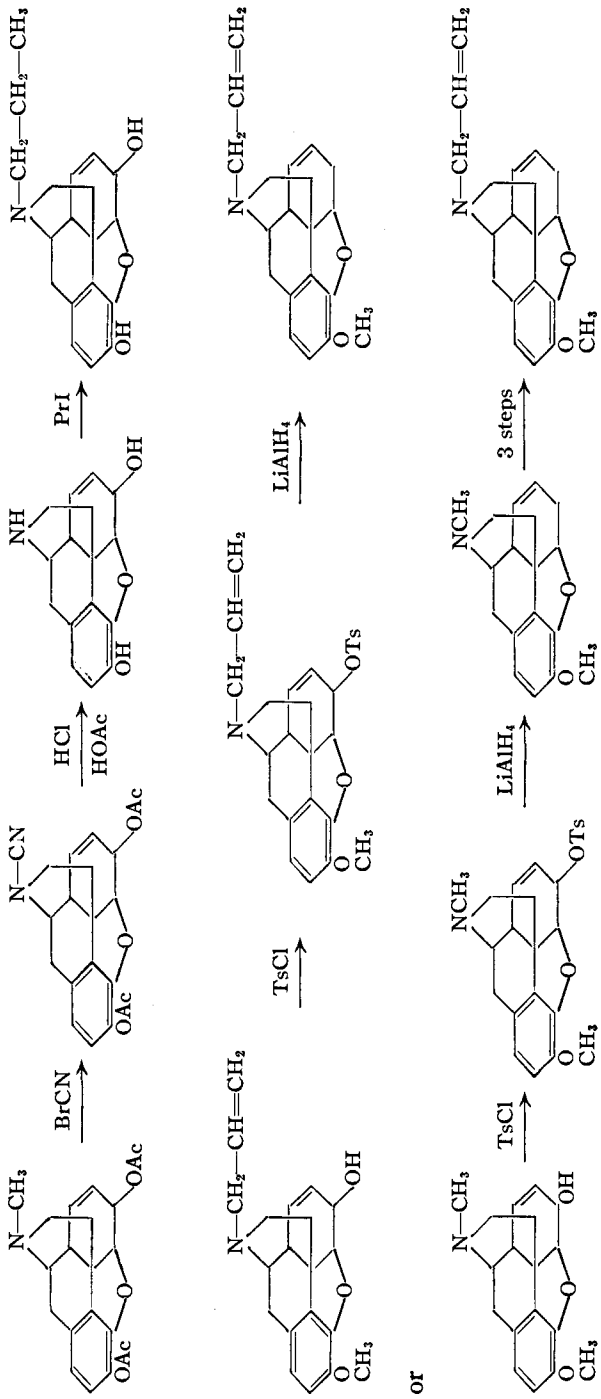


I

phine and the other potent analgesics is now well-known.[1] Since this remarkable property is of practical value[2] as well as theoretical, we have been prompted to prepare and examine other variants of the N-substituent in morphine and related alkaloids.

Interestingly enough, prior to this study almost no substituted normorphines had been reported. The notable exceptions are N-cyanonormorphine,[3] N-nitrosonormorphine,[4] O,O′,N-triacetylnormorphine,[3] N-carbamylnormorphine[5] and N-phenylthiocarbamylnormorphine.[3] In the codeine series, however, a large number of N-alkyl derivatives has been prepared.[6] In addition to some 30 variously N-substituted normorphines, another score of new compounds was derived from related epoxymorphinans. These include the dihydro-, desoxy- and dihydrodesoxynormorphine series plus various dihydronormorphinones.

Most of the compounds were prepared directly by alkylation of the corresponding normorphines. In the preparation of these normorphines the methyl group on the nitrogen atom was replaced by hydrogen by reaction with cyanogen bromide followed by hydrolysis with acid.[3] Using N-propylnormorphine as an example these steps can be illustrated as



The alcoholic oxygen function was removed to form the desoxy- and dihydrodesoxy compounds by

(1) J. Weijlard and A. E. Erickson, THIS JOURNAL, **64**, 869 (1942); K. Unna, *J. Pharmacol. Exptl. Therap.*, **79**, 27 (1943); C. C. Smith, E. G. Lehman and J. L. Gilfillan, *Federation Proc.*, **10**, 335 (1951); R. A. Huggins, W. G. Glass and A. R. Bryan, *J. Pharmacol. Exptl. Therap.*, **101**, 19 (1951); E. R. Hart and E. L. McCawley, *ibid.*, **82**, 339 (1944); L. M. Radoff and S. E. Huggins, *Proc. Soc. Exp. Biol. Med.*, **78**, 879 (1951).

(2) J. E. Eckenhoff, J. D. Elder and B. D. King, *Am. J. Med. Sci.*, **222**, 115 (1951); **223**, 191 (1952); H. F. Fraser, A. Wikler, A. J. Eisenman and H. Isbell, *J. Am. Med. Assoc.*, **148**, 1205 (1952); J. E. Eckenhoff, G. L. Hoffman and R. D. Dripps, Presented at the Annual Meeting of the Am. Soc. of Anesthesiologists, Wash., D. C., Nov. 8, 1951.

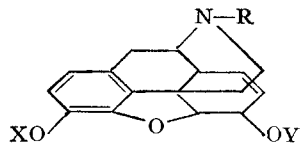
(3) J. v. Braun, O. Kruber and E. Aust, *Ber.*, **47**, 2312 (1914).

(4) E. Speyer and L. Walther, *ibid.*, **63**, 852 (1930).

(5) S. Weil and S. Rozenblumowna, *C. A.*, **29**, 5920 (1935).

(6) J. v. Braun, *Ber.*, **49**, 977 (1916); *ibid.*, **49**, 2655 (1916); J. v. Braun, M. Kuhn and S. Siddigui, *ibid.*, **59**, 1081 (1926).

TABLE I



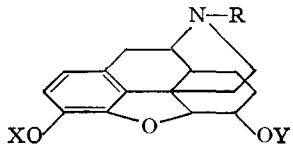
SUBSTITUTED NORMORPHINES

R	X	Y	Method	Formula	Organic halide	Solvent of reflux	Time of reflux in hr.	Recrystallizing solvent	M.p., °C.	$[\alpha]^{23}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_2CH_3	H	H	A	$C_{18}H_{21}NO_3$	I	EtOH	7	EtOAc	217–218	−146°	72.71	72.12	7.07	6.95
CH_2CH_2OH	H	H	A	$C_{18}H_{21}NO_4$	Br	PrOH	22	EtOH	246–247	−142	68.50	68.31	6.71	6.78
CH_2CONH_2	H	H	[a]	$C_{18}H_{20}N_2O_4$				NaOH–HOAc	303–304	[b]	65.84	65.80	6.14	5.96
CH_2COOEt	H	H	A	$C_{20}H_{23}NO_5 + 2\%H_2O$[c]	Br	EtOH	4	EtOH	127–129	−121	65.86	66.12	6.70	6.51
$CH_2CH_2OC_6H_5$	H	H	A	$C_{24}H_{25}NO_4$	Br	PrOH	26	MeOH	186–187	−126	73.64	73.72	6.44	6.27
$CH_2CH{=}CH_2$	Ac	Ac	C	$C_{23}H_{25}NO_5 \cdot C_4H_6O_6 \cdot {}^1/_2H_2O$				H_2O	148–155	−126	58.44	58.18	5.82	5.81
$CH_2CH{=}CH_2$	Ac	H	F	$C_{21}H_{23}NO_4 \cdot {}^1/_2H_2O$[d]				MeOH	105–107	−194	69.60	69.47	6.67	6.95
$CH_2CH{=}CH_2$ N-Oxide	H	H	[e]	$C_{19}H_{21}NO_4 \cdot {}^1/_2H_2O$				H_2O–EtOH	247	−104	68.05	68.12	6.62	6.89
$CH_2CH{=}CH_2 \cdot CH_3Br$	H	H	[f]	$C_{20}H_{24}NO_3Br \cdot H_2O$				H_2O	249–250	− 63	56.61	56.87	6.18	6.29
$CH_2CBr{=}CH_2$	H	H	A	$C_{19}H_{20}NO_3Br \cdot HBr$	Br	EtOH	24	MeOH	265	− 85	48.43	48.19	4.49	4.54
$CH_2CH_2CH_3$	Ac	Ac	C	$C_{23}H_{27}NO_5$				EtOH	135–136	−177	69.50	69.26	6.85	6.85
$CH_2CH_2CH_3$	CH_3	H	A[g]	$C_{20}H_{25}NO_3 \cdot HCl$	I	EtOH	4	EtOH	276–278	−103	66.01	66.13	7.20	7.25
$CH(CH_3)_2$	H	H	A	$C_{19}H_{23}NO_3 \cdot HClO_4$	Br	PrOH	8	EtOH	275	− 97	55.14	55.46	5.85	5.66
$CH_2CH_2CH_3$	H	H	A	$C_{19}H_{23}NO_3 \cdot HCl + 4\%H_2O$[h]	I	EtOH	20	H_2O	195–198	− 94	62.64	62.59	7.08	6.81
$CH(CH_3)_2$	CH_3	H	A	$C_{20}H_{25}NO_3 \cdot HBr$	I	EtOH	20	EtOH	237–238	− 86	58.83	59.12	6.42	6.19
CH_2CH_2CN	H	H	A	$C_{19}H_{20}N_2O_3$	Br	EtOH	20	EtOH	220–221	−146	70.36	70.65	6.22	6.22
CH_2COCH_3	H	H	A	$C_{19}H_{21}NO_4$	Cl	$HCONMe_2$	3	EtOH	170–172	−137	69.71	69.95	6.47	6.30
$CH_2CHOHCH_3$	H	H	A[i]	$C_{19}H_{23}NO_4 \cdot HBr$	Br	PrOH	44	EtOH	241–243	− 96	55.61	55.57	5.90	5.66
$CH_2CH_2CH_2OH$	H	H	A	$C_{19}H_{23}NO_4 \cdot HCl \cdot H_2O$	Br	PrOH	48	H_2O	207–210	− 85	59.44	59.23	6.83	6.67
CH_2CH_2COOEt	H	H	A	$C_{21}H_{25}NO_5$	Br	EtOH	4	MeOH	155–157	−129	68.07	68.17	6.78	6.64
$CH_2C(CH_3){=}CH_2$	H	H	A	$C_{20}H_{23}NO_3$	I	EtOH	10	EtOH	196–199[j]	−152	73.83	73.89	7.12	6.90
					Cl	EtOH	74	Me_2CO–H_2O						
$CH_2CH{=}CHCH_3$	H	H	A	$C_{20}H_{23}NO_3 \cdot C_4H_6O_6$	Cl	EtOH	104	EtOH	171–173	− 74	60.63	60.56	6.15	6.43
$CH_2CH(CH_3)_2$	H	H	A	$C_{20}H_{25}NO_3$	I	PrOH	24	EtOH	209–210	−140	73.39	73.36	7.70	7.50
$CH_2CH(CH_3)_2$	CH_3	H	A	$C_{21}H_{27}NO_3 \cdot HBr$	I	EtOH	18	EtOH	265–268	− 96	59.73	59.83	6.68	6.93
$CH_2(CH_2)_2CH_3$	H	H	A	$C_{20}H_{25}NO_3$	Br	PrOH	30	EtOH	200–202	−139	73.39	73.26	7.70	7.59
$CH_2(CH_2)_3CH_3$	H	H	A	$C_{21}H_{27}NO_3$	Br	PrOH	20	EtOH	202–203	−132	73.87	73.90	7.97	7.96
$CH_2(CH_2)_4CH_3$	H	H	A	$C_{22}H_{29}NO_3$	Br	PrOH	22	C_6H_6	181–182	−118	74.34	74.44	8.22	7.96
				$C_{22}H_{29}NO_3 \cdot HCl$				EtOH–MeOH	284	− 89	67.42	67.28	7.72	7.46
$CH_2C_6H_5$	H	H	A	$C_{23}H_{23}NO_3$	Cl	EtOH	20	EtOH	230–231	−130	76.44	76.65	6.41	6.17
$CH_2C_6H_4NO_2$-*p*	H	H	A[i]	$C_{23}H_{22}N_2O_5$	Cl	EtOH	21	EtOH	232–233	− 95	67.97	67.96	5.46	5.53
$CH_2COC_6H_5$	H	H	A	$C_{24}H_{23}NO_4 \cdot HCl \cdot 1{}^1/_2H_2O$	Cl	EtOH	65	H_2O	235–239	− 85	63.65	63.66	6.01	6.01
$CH_2CH_2C_6H_5$	H	H	A	$C_{24}H_{25}NO_3 \cdot C_4H_6O_6 + 2.5\%H_2O$[k]	Br	EtOH	72	EtOH–H_2O	146–148	− 67	62.39	62.47	6.07	6.03
$CH_2CH_2C_6H_{11}$	H	H	A	$C_{24}H_{31}NO_3 \cdot C_4H_6O_6 \cdot {}^1/_2H_2O$	Br	EtOH	44	MeOH–H_2O	156–159	− 61	62.20	62.40	7.09	7.32
COEt	COEt	COEt	C	$C_{25}H_{29}NO_6$				EtOH	215–217	−260	68.33	68.59	6.65	6.40

[a] Obtained from ester using aqueous ammonium hydroxide at room temperature. [b] Too insoluble for rotation. [c] Found: H_2O, 2.2%. [d] Calcd. for monoacetyl 12.49, found 11.87. [e] Obtained by treating an acetic acid solution of N-allylnormorphine with 30% hydrogen peroxide at 60–70° for two hours. After standing overnight the solution was made alkaline with ammonia and the product slowly crystallized. [f] Obtained by warming a methanol solution of morphine and allyl bromide on the steam-bath for ten minutes and then allowing to stand at room temperature. [g] The product extracted from an alkaline solution; J. v. Braun[6] lists melting point as 185°. [h] Found: H_2O, 4%. [i] Extracted product using ether in a Soxhlet apparatus. [j] One preparation yielded an analytically pure polymorphic form, m.p. 216°. [k] Found: H_2O, 2.3%.

rize, however, by the statement that given a free phenolic group at C_3, substitution of allyl, methallyl, *n*-propyl or isobutyl for methyl in all five series invariably produced compounds capable of counteracting the analgesic effect of morphine. Despite trial of numerous other substituents, both close and very distant in relationship to these four, no other grouping was found which imparted significant morphine antagonizing properties. Some of these were inert while others had analgesic action. Acetylation (mono or di) of the active antagonists sometimes yielded derivatives essentially as active as

TABLE II

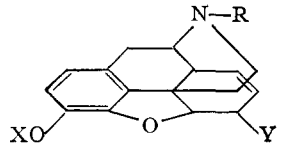


SUBSTITUTED DIHYDRONORMORPHINES

R	X	Y	Method	Formula	Recrystallizing solvent	M.p., °C.	$[\alpha]^{23}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$CH_2CH{=}CH_2$	H	H	A[a]	$C_{19}H_{23}NO_3$	EtOAc	179–180	−170°	72.81	73.08	7.40	7.26
				$C_{19}H_{23}NO_3 \cdot HBr$	EtOH–Et_2O	264–266	−113	57.88	58.08	6.13	6.25
$CH_2CH{=}CH_2$	CH_3	H	A[b]	$C_{20}H_{25}NO_3 \cdot HBr$	EtOH	221–223	−116	58.83	59.10	6.42	6.14
$CH_2CH{=}CH_2$	Ac	Ac	C	$C_{23}H_{27}NO_5 \cdot C_4H_6O_6 \cdot {}^1/_2H_2O$	EtOH	107–113	− 76	58.37	58.55	6.17	6.35
$CH_2CH_2CH_3$	H	H	B	$C_{19}H_{25}NO_3$	EtOAc	231–232	−150	72.35	72.46	7.99	7.87
				$C_{19}H_{25}NO_3 \cdot HCl \cdot H_2O$	EtOH	147–149	−114	61.69	61.93	7.63	7.47
$CH_2CH_2CH_3$	CH_3	H	B	$C_{20}H_{27}NO_3 \cdot HBr$	EtOH	283–285	−106	58.54	58.52	6.88	6.58
$CH_2CH_2CH_3$	Ac	Ac	C	$C_{23}H_{29}NO_5 \cdot HCl$	EtOH–Et_2O	262–266	− 96	63.37	63.48	6.94	6.90
$CH_2C(CH_3){=}CH_2$	H	H	A[c]	$C_{20}H_{25}NO_3$	EtOH	181–182	−159	73.37	73.32	7.70	7.22
$CH_2CH(CH_3)_2$	H	H	B	$C_{20}H_{27}NO_3$	EtOH	191–193	−156	72.93	72.85	8.26	8.17

[a] Allyl bromide was refluxed 17 hours in ethanol. [b] Allyl bromide was refluxed 18 hours in ethanol. [c] Methallyl iodide was refluxed 6 hours in ethanol.

TABLE III



SUBSTITUTED DESOXYNORMORPHINES

R	X	Y	Method	Formula	Recrystallizing solvent	M.p., °C.	$[\alpha]^{23}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_3	H	E and G[a]	$C_{17}H_{19}NO_2 \cdot HBr$	EtOH	311–312	− 23°	58.29	58.42	5.76	5.49
$CH_2CH{=}CH_2$	H	H	D	$C_{19}H_{21}NO_2$	EtOAc	174–175	− 96	77.27	77.57	7.17	7.46
				$C_{19}H_{21}NO_2 \cdot HCl$	EtOH–Et_2O	297–300	− 60	68.76	68.64	6.69	6.85
$CH_2CH{=}CH_2$	CH_3	H	E also A[b]	$C_{20}H_{23}NO_2$	Et_2O	75– 77	− 98	77.63	77.93	7.49	7.36
$CH_2CH{=}CH_2$	CH_3	Ts	E	$C_{27}H_{29}NO_5S$	Et_2O	109–110	−183	67.63	67.77	6.10	6.09
				$C_{27}H_{29}NO_5S \cdot HBr$	MeOH	145–146	−163	57.85	57.85	5.40	5.31
$CH_2CH_2CH_3$	H	H	D	$C_{19}H_{23}NO_2 \cdot HCl + 3.5\%H_2O$[c]	H_2O	272–273	− 33	65.97	66.10	7.37	7.01
$CH_2CH_2CH_3$	CH_3	H	A[d]	$C_{20}H_{25}NO_2 \cdot HBr$	EtOH–Et_2O	281–283	− 34	61.23	60.93	6.68	6.88

[a] Rapoport[7] reported the N-cyanodesoxynorcodeine. [b] Allyl bromide refluxed 5 hours in ethanol. [c] Found: H_2O, 3.7%. N-Propyldesoxynormorphine separated as a crystalline solid when the pyridine hydrochloride solution was poured into water. [d] *n*-Propyl iodide was refluxed 24 hours in ethanol.

extension of the elegant procedure recently reported by Rapoport and by Karrer, tosylation followed by lithium aluminum hydride reduction.[7] This can be accomplished either before or after the N-alkylation, for example, N-allyldesoxynorcodeine can be prepared by either of these two methods. Details of procedure and characterization are presented in the tables and Experimental section.

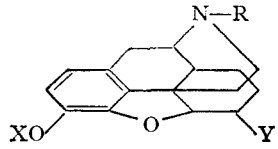
All compounds were examined both for analgesic and morphine reversing activity; the pharmacological findings will be reported in detail by Dr. C. A. Winter and his collaborators of the Merck Institute for Therapeutic Research. We may summarize the starting materials, while in other instances the products were less active. Masking of the phenolic hydroxyl by methyl invariably produced less active substances and sometimes completely inert products.

To see if the reversal of the analgesic activity is entirely general when the allyl group is substituted for the methyl group, several other analgesic compounds were converted to the N-allyl derivatives. In most cases the compounds retained some of their analgesic activity while none became morphine antagonists. The compounds which were converted to the N-allyl derivatives were: meperidine,[8] dihydrothebainone methyl ether (also to

(7) H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951); P. Karrer and G. Widmark, *Helv. Chim. Acta*, **34**, 34 (1951).

(8) R. H. Thorpe and E. Walton, *J. Chem. Soc.*, 559 (1948).

TABLE IV

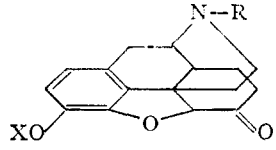


SUBSTITUTED DIHYDRODESOXYNORMORPHINES

R	X	Y	Method	Formula	Recrystallizing solvent	M.p., °C.	$[\alpha]^{23}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_3	H	G[a] and B	$C_{17}H_{21}NO_2$	EtOAc	92–94	− 71°	75.26	75.50	7.80	7.60
$CH_3CH{=}CH_2$	H	H	D	$C_{19}H_{23}NO_2$	EtOAc	141–142	−102	76.74	76.86	7.79	7.62
$CH_3CH{=}CH_2$	CH_3	H	A[b]	$C_{20}H_{25}NO_2$	EtOAc	72–74	−106	77.11	77.11	8.09	7.81
$CH_3CH{=}CH_2$	CH_3	Ts	E	$C_{27}H_{31}NO_5S\cdot C_4H_6O_4\cdot{}^1/_2H_2O$	EtOH	135–140	−112	58.12	58.03	5.98	6.21
$CH_3CH_2CH_3$	H	H	D	$C_{19}H_{25}NO_2$	EtOAc	141–144	− 92	76.20	76.20	8.42	8.39
$CH_2CH_2CH_3$	CH_3	H	E and B[c]	$C_{20}H_{27}NO_2\cdot HBr$	EtOH	282–283	− 62	60.93	61.21	7.16	6.86

[a] Rapoport[7] reported the N-cyanodesoxynorcodeine. [b] Allyl bromide refluxed 5 hours in ethanol. [c] Prepared from N-allyl-6-tosylnorcodeine.

TABLE V



SUBSTITUTED DIHYDRONORMORPHINONES

R	X	Method	Formula	Recrystallizing solvent	M.p., °C.	$[\alpha]^{23}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_3	G	$C_{17}H_{19}NO_3$	EtOAc	144–147	−176°	71.56	71.45	6.71	6.71
CN	CH_3	G	$C_{18}H_{18}N_2O_3$	EtOH	217–218	−250	69.65	69.73	5.84	5.96
$CH_2CH{=}CH_2$	H	D	$C_{19}H_{21}NO_3$	EtOAc	212–216	−200	73.28	73.43	6.80	6.86
$CH_2CH{=}CH_2$	CH_3	A[a]	$C_{20}H_{23}NO_3\cdot C_4H_6O_6\cdot H_2O$	EtOH	106–110	− 84	58.50	58.72	6.32	6.27
$CH_2CH_2CH_3$	H	D	$C_{19}H_{23}NO_3$	EtOAc	214–216	−155	72.83	72.76	7.40	7.70
$CH_2CH_2CH_3$	CH_3	A[b]	$C_{20}H_{25}NO_3\cdot HBr$	MeOH	293	−135	58.83	58.99	6.42	6.47
$CH_2C(CH_3){=}CH_2$	H	D	$C_{20}H_{23}NO_3\cdot C_4H_6O_4\cdot{}^1/_2H_2O$	EtOH–H_2O	119–124	− 97	59.50	59.31	6.24	6.67
$CH_2C(CH_3){=}CH_2$	CH_3	A[c]	$C_{21}H_{25}NO_3\cdot C_4H_6O_6\cdot H_2O$	EtOH–H_2O	88– 92	− 98	59.17	59.40	6.56	6.90
$CH_2CH(CH_3)_2$	H	D	$C_{20}H_{25}NO_3\cdot C_4H_6O_6$	EtOH	137–140	− 89	60.37	60.50	6.55	6.99
$CH_2CH(CH_3)_2$	CH_3	A[d]	$C_{21}H_{27}NO_4\cdot C_4H_6O_6 + 3\%H_2O$[e]	EtOH–H_2O	98–100	− 97	59.29	59.47	6.90	6.57

[a] Allyl bromide refluxed 6 hours in ethanol. [b] Propyl iodide refluxed 30 hours in ethanol. [c] Methallyl chloride refluxed 70 hours in ethanol. [d] Isobutyl iodide refluxed 70 hours in ethanol. [e] Found: H_2O, 3.3%.

the N-propyl derivative) and N-methyl-Δ^6-dehydroisomorphinan.[9] N-Methylisomorphinan, essentially without analgesic activity, yielded an inert N-allyl compound.[9] Inactivity of the two isomorphinans is of particular note in view of the recent announcement that N-allyl-3-hydroxymorphinan is a potent morphine antagonist.[10]

Experimental

The physical data for the compounds prepared are given in the tables. Examples of general methods used in their preparation are as follows:

A. Reaction of Normorphine or Derivatives with an Organic Halide.—A mixture of 6 g. (0.022 mole) of normorphine, 0.022 mole of organic halide and 2.68 g. (0.032 mole) of sodium bicarbonate in 100 ml. of solvent was stirred under reflux for an extended length of time. The mixture was filtered hot from precipitate containing some unchanged normorphine and inorganic material. The filtrate was evaporated to dryness and the residue extracted with hot chloroform. This extraction usually dissolved the product leaving any further normorphine and inorganic material behind. The chloroform solution was then concentrated to near dryness and triturated with ether, usually giving the N-substituted normorphines as amorphous solids (a small amount often dissolved in the ether triturate) which were crystallized as the free bases or as acid salts. When norcodeine was used instead of normorphine a chloroform extraction also dissolved unchanged norcodeine so it was necessary to remove it by crystallization.

B. Hydrogenation of double bonds was carried out in 50% acetic acid solution using 40 p.s.i. pressure of hydrogen with palladium chloride as the catalyst.

C. Acylation was accomplished by heating the morphine derivative with an acid anhydride for about two hours at 100°. The excess anhydride was removed in a vacuum and the product crystallized either as the free base or as an acid salt.

D. Cleavage of the methyl ethers in the conversion of codeine compounds to morphine compounds was performed using pyridine hydrochloride at 210–225°.[11]

E. Tosylation and Removal of Tosyl Groups.—The 6-tosyl compounds were prepared and then converted into the 6-desoxy compounds by reaction with lithium aluminum hydride.[7]

F. Selective Deacetylation.—The monoacetyl derivative of N-allylnormorphine was obtained by allowing the diacetyl derivative to stand with twice its weight of 2.5 *N* hydrochloric acid for five hours. The solution was then made basic with ammonium hydroxide and the monoacetyl derivative isolated by fractional crystallization.

G. N-Demethylation.—The methyl group on the nitrogen was replaced by hydrogen by treatment with cyanogen bromide followed by hydrolysis with the acid.[8] The yield of crude product in the condensation of an organic halide with a normorphine ranged between 25 and 80%, and of purified product between 5 and 50%. The rotations were taken with approximately 1% alcohol solutions.

N-Allyldihydrothebainone methyl ether, prepared by methods G and A was isolated as a hydrobromide, m.p. 275–278°, $[\alpha]^{23}D$ −53°.

Anal. Calcd. for $C_{20}H_{27}NO_3\cdot HBr$: C, 59.71; H, 6.68. Found: C, 59.68; H, 6.67.

Similarly the N-propyl derivative was isolated as a perchlorate, m.p. 268–270°, $[\alpha]^{23}D$ −49°.

(9) Unpublished information supplied by Dr. H. D. Brown of these laboratories.

(10) W. M. Benson, E. O'Gara and S. Van Winkle, *J. Pharmacol. Exper. Therap.*, **106**, 373 (1952).

(11) H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 5485 (1951).

Anal. Calcd. for $C_{21}H_{29}NO_3 \cdot HClO_4$: C, 56.82; H, 6.81. Found: C, 56.98; H, 6.55.

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RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO.]

Tetrakis-(trifluoromethyl)-biphenyls

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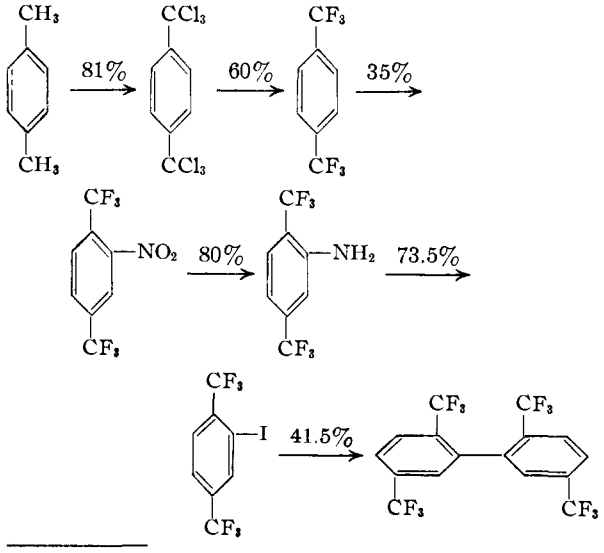
2,2',5,5'-Tetrakis-(trifluoromethyl)-biphenyl and 3,3',5,5'-tetrakis-(trifluoromethyl)-biphenyl have been synthesized, and their ultraviolet absorption spectra have been determined.

For applications requiring a dielectric constant in excess of four, the dielectrics most commonly used are the chlorinated biphenyls and naphthalenes. These materials are of limited stability in an electric field, particularly at elevated temperatures. In most respects, trifluoromethyl groups are desirable replacements for the chlorine groups. They have a relatively large dipole moment,[1] and are very stable chemically, except when ortho or para to a strongly ortho–para directing group.[2]

The only trifluoromethyl substituted biphenyls which have been prepared and characterized are the 3-trifluoromethylbiphenyl,[3] 3,3'-bis-(trifluoromethyl)-biphenyl,[3,4] and 4,4'-bis-(trifluoromethyl)-biphenyl.[4,5] Since the trifluoromethyl group has a large positive σ-constant,[1] an iodobenzene containing two trifluoromethyl groups should undergo the Ullmann reaction. We have taken advantage of this consideration to prepare 3,3',4,4'-tetrakis-(trifluoromethyl)-benzene and 2,2',5,5'-tetrakis-(trifluoromethyl)-benzene. The reaction sequence shown below was used to prepare the latter compound and a completely similar reaction sequence resulted in the former.



The ultraviolet absorption spectra of the two tetrakis-(trifluoromethyl)-biphenyls are of interest. These are presented in Fig. 1, in which the spectra of benzotrifluoride, 1,4-bis-(trifluoromethyl)-benzene and 3,3'-bis-(trifluoromethyl)-biphenyl are included for purposes of comparison.

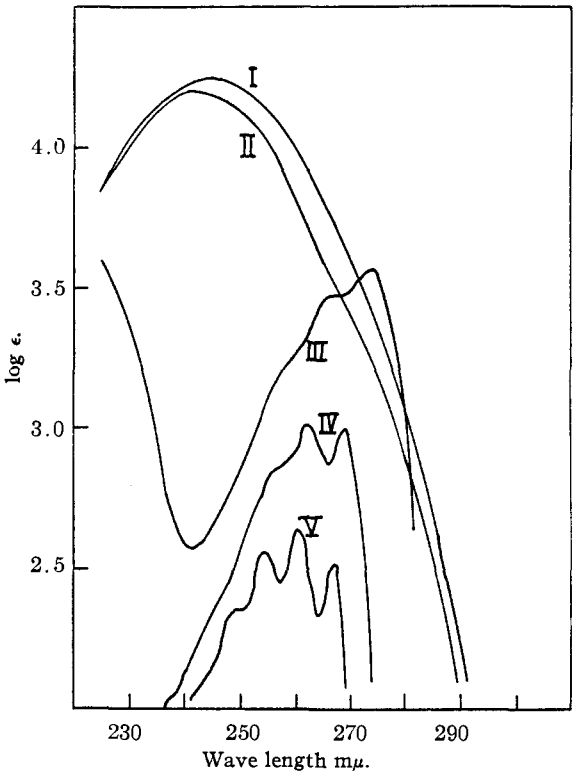


Fig. 1.—Ultraviolet absorption spectra of trifluoromethyl substituted compounds in 2,2,4-trimethylpentane: I, 3,3'-bis-(trifluoromethyl)-biphenyl; II, 3,3',5,5'-tetrakis-(trifluoromethyl)-biphenyl; III, 2,2',5,5'-tetrakis-(trifluoromethyl)-biphenyl; IV, 1,4-bis-(trifluoromethyl)-benzene; V, benzotrifluoride.

Benzotrifluoride (log ϵ_{max} 2.6 at 260 mμ)[6] shows

(1) J. D. Roberts, R. L. Webb and E. A. McElhill, THIS JOURNAL, **72**, 408 (1950).
(2) R. G. Jones, *ibid.*, **69**, 2346 (1947).
(3) C. K. Bradsher and J. B. Bond, *ibid.*, **71**, 2659 (1949).
(4) M. Markarian, *ibid.*, **74**, 1858 (1952).
(5) S. D. Ross and I. Kuntz, *ibid.*, **74**, 1297 (1952).

(6) This spectrum is in excellent agreement with that reported by C. H. Miller and H. W. Thompson for benzotrifluoride in *n*-heptane; *J. Chem. Phys.*, **17**, 845 (1949).