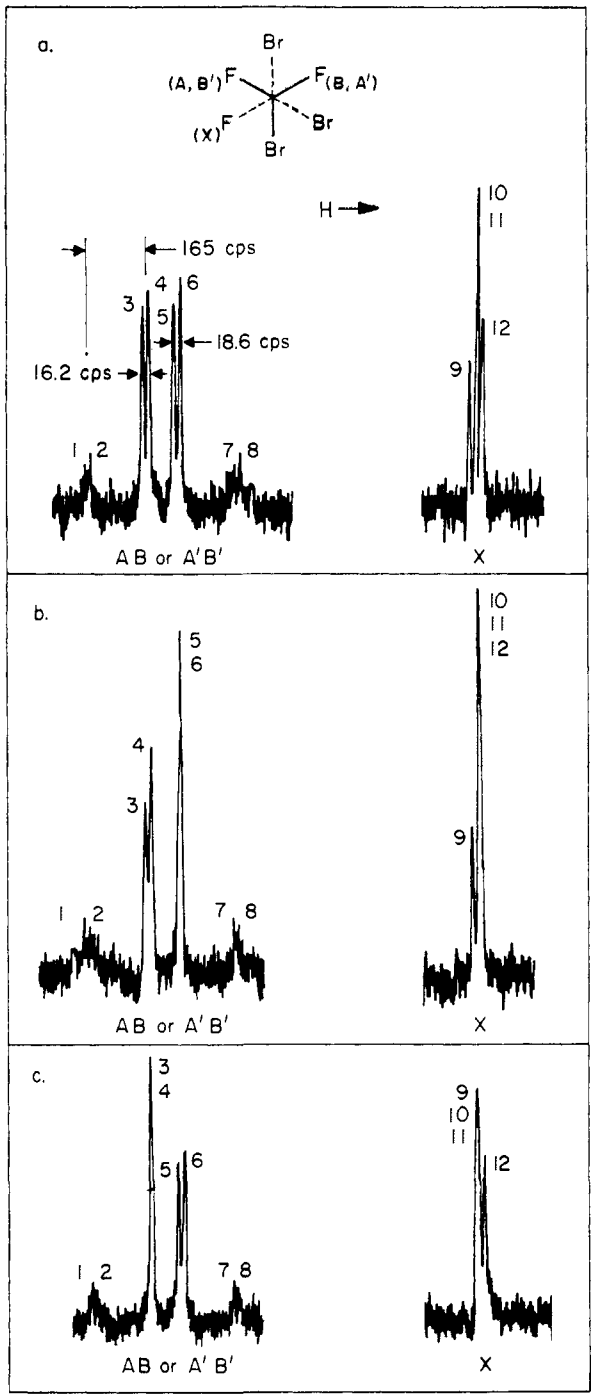

Fig. 1.—The low temperature (−110°) F^{19} n.m.r. spectrum of 1,1,2-trifluoro-1,2,2-tribromoethane (50% in CS_2): a, undecoupled; b, decoupled, $\gamma H_1/2\pi$ = 25 cps. and Ω = 670 cps.; c, decoupled, $\gamma H_1/2\pi$ = 25 cps. and Ω = 756 cps.

have different signs lines 10 and 12 should collapse (as observed in Figure 1b).

When decoupling at 756 cps. and observing the AB region, lines 9 and 10 are strongly irradiated when lines 3 and 4 are being observed. If J_{BX} and J_{AB} have the same relative signs then lines 3 and 4 should not collapse, but if the signs of J_{BX} and J_{AB} are different, lines 3 and 4 should collapse (as observed in Fig. 1c). On observing the X region at the same decoupling frequency, lines 11 and 12 should collapse if J_{AB} and J_{BX} have the same relative signs, but if J_{AB} and J_{BX} have different signs then lines 9 and 10 should collapse (as observed in Fig. 1c).

The fact that the presence of Ic was detected and that the *gauche* coupling constant in this A_2X system is about 18.8 cps. enables us to unambigously assign $J_{A'X}$ = 16.2 cps. (the *trans* coupling) and assign $J_{B'X}$ = 18.6 cps. (the *gauche* coupling) in rotational configurations Ia and Ib. The significance of the difference in the magnitudes of the *trans* and *gauche* couplings is being further investigated.

The results of the double resonance experiments on I reported here show unequivocally that J_{AB}, the geminal coupling constant, has a different relative sign from that of $J_{A'X}$ and $J_{B'X}$, the vicinal coupling constants. Thus, the same degree of caution should be exercised in the analyses of F^{19} n.m.r. spectra as is required in the analyses of H^1 n.m.r. spectra where it has recently been demonstrated that likewise the geminal H^1–H^1 coupling constant has a different relative sign than the vicinal H^1–H^1 coupling constants.[8,9]

(8) R. R. Fraser, R. U. Lemieux and J. D. Stevens, *J. Am. Chem. Soc.*, **83**, 3901 (1961).

(9) F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4667 (1961).

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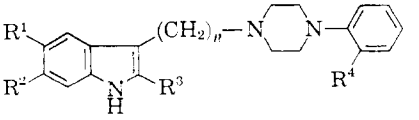
RECEIVED FEBRUARY 12, 1962

1-(INDOLYLALKYL)-4-ARYLPIPERAZINES: A NEW CLASS OF TRANQUILIZERS

Sir:

Hiebel[1] probably was the first to suggest that the tranquilizing effect of chlorpromazine derives from its central adrenolytic action. It occurred to us to see whether by appropriate modification, other adrenolytic agents could be transformed to central nervous system depressant drugs. Since we had available from other studies 1-phenylpiperazine, which has been reported to be a relatively weak adrenolytic,[2] we prepared and studied a series of compounds represented by formula I.[3] The in-



I

II, R^1, R^2 = OCH_3, R^3 = CH_3, R^4 = H, n = 2
III, R^1, R^2, R^4 = H, R^3 = CH_3, n = 2
IV, R^1, R^2 = O–CH_2–O, R^3 = H, R^4 = OCH_3, n = 2
V, R^1, R^2, R^3, R^4 = H, n = 1

dolylalkyl group was selected because of its relationship to serotonin,[4] a normal constituent of the

(1) G. Hiebel, M. Bonvallet and P. Dell, *Semaine hôp. Paris*, **30**, 2346 (1954); *cf.* D. Bovet, ref. 4.

(2) D. Bovet and F. Bovet-Nitti, "Médicaments du Système Nerveux Végétatif," S. Karger, S. A., Bale, 1948, p. 246.

(3) Analyses of all new compounds were satisfactory. These were performed by Mr. K. D. Fleischer and staff of this Institute.

(4) Since norepinephrine normally is present in the brain too, and certain phenethylamines (*e.g.*, mescaline) show central nervous sys-

brain and to bufotenin and its congeners which are centrally active indoles.[5]

A large number of derivatives of I ($n = 2$) were prepared by an adaptation of the method of Speeter and Anthony[6] and by condensation of indolylalkanoic acids with the required phenylpiperazines followed by reduction where $n > 2$. These compounds were examined in some detail biologically. Maximum CNS-depressant activity was observed when the methylene bridge contained two or three carbon atoms and the indole nucleus was substituted by 2-methyl and 5,6-dimethoxy groups (I, $n =$ 2 or 3, $R^1,R^2 = OCH_3$, $R^3 = CH_3$). An *o*-methoxy substituent in the phenyl ring generally caused an increase in peripheral adrenolytic activity without a concomitant increase in central effects. Some of the relevant pharmacological properties of a few representative members are summarized in Table I. The values for chlorpromazine (CPZ) are included for reference.

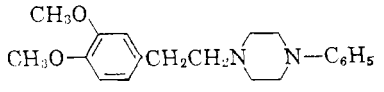
TABLE I

Test procedure[a]	II	III	IV	V	CPZ
Hexobarbital potentiation[b]	3.7	5.0	8.2	>128	4.4
Head withdrawal reflex[c]	6.5	>128	10.0	>128	8.0
Adrenolytic activity[d]	106	55	12.0	>800	44
Decrease in spontaneous activity[e]	0.56	3.7	7.1	45	4.7

[a] Results are expressed as ED_{50} values in mg./kg. p.o. except for adrenolytic data which are given as γ/kg. i.v. [b] D. W. Wylie, *Proc. Soc. Exp. Biol. Med.*, **98**, 716 (1956). [c] D. W. Wylie, *J. Pharmacol. Exp. Therap.*, **127**, 276 (1959); R. C. Rathbun, *et al.*, *ibid.*, **122**, 64A (1958). [d] F. P. Luduena, E. O'Malley and I. A. Oyen, *Arch. Intern. Pharmacodynamie*, **122**, 111 (1959). [e] L. S. Harris and F. C. Uhle, *J. Pharmacol. Exp. Therap.*, **132**, 251 (1961).

Although there was no quantitative correlation in this series between adrenolytic and central nervous system depressant activities (*cf.* II *vs.* IV),[7] compounds such as V which are essentially inactive as adrenolytic drugs are also relatively inactive in the CNS tests. Our observations tend to support the hypothesis[1,3] that tranquilizing activity is associated with peripheral adrenolytic action.

tem activity we started a parallel study in this series. Preliminary biological evaluation indicated that (i) was much less interesting than its indole counterpart. During the course of our work the Lilly



(i)

group (J. Mills, *et al.* Abstracts of the 132nd Meeting of the Amer. Chem. Soc., New York, N. Y., Sept. 8–13, 1957, p. 60, *et seq.*) generalized and developed Hiebel's original suggestion (ref. 1) and was able to show that a variety of chemically distinct adrenolytic agents can be converted to psychosedative drugs. One of these was (i). Mills, *et al.* seemed to focus their attention on modification of the 1,4-benzodioxanes, in particular, ethoxybutamoxane (2-dibutylaminomethyl-8-ethoxy-1,4-benzodioxane). Independently the area was explored by Bovet and his colleagues (see D. Bovet, *Gazz. chim. Ital.*, **89**, 196 (1959), and also by Boissier (J. R. Boissier, *et al.*, *Arch. Int. Pharmacodyn.*, **133**, 29 (1961)).

(5) E. Evarts, *Arch. Neurol. and Psychiat.*, **75**, 49 (1956); W. J. Turner and S. Merlis, *ibid.*, **81**, 121 (1959).

(6) N. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6209 (1954).

(7) This may be due to the differences in accessibility to the receptor sites in the central nervous system. The generic name for IV is solypertine.

Further studies with II (generic name, oxypertine) showed that low oral doses produced taming in untrained Rhesus monkeys while at higher doses sedation and catalepsy were observed. Unlike chlorpromazine, II did not potentiate the analgesic action of either morphine or meperidine. On the other hand, II like chlorpromazine, did act as a potent anti-emetic, and in rats did not release serotonin from either brain or heart. It did release norepinephrine from the heart[8]; so that II appears unique in that it can both release and block the action of norepinephrine.

Acknowledgement.—We wish to thank Miss L. Polak and J. MacAuliff for technical assistance.

(8) Private communication from Dr. S. Spector and Dr. A. Sjoerdsma of the National Heart Institute.

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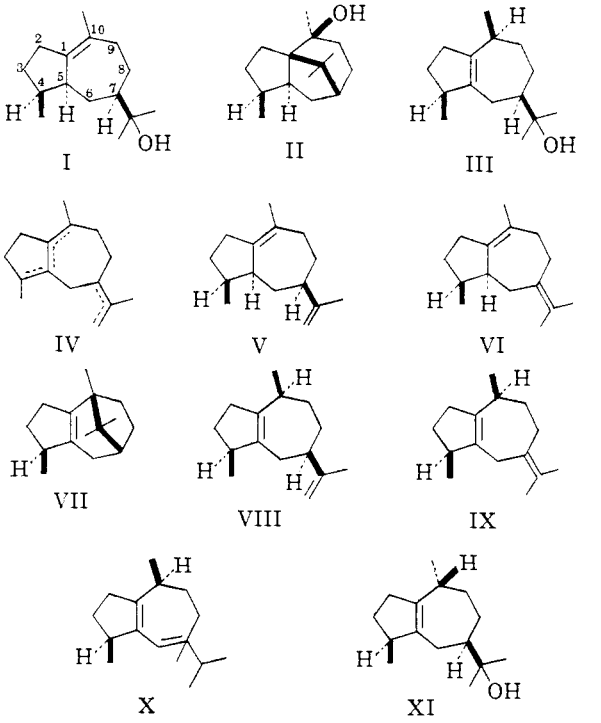
RECEIVED FEBRUARY 6, 1962

CONVERSION OF BULNESOL TO PATCHOULI ALCOHOL, GUAIOL, AND "δ-GUAIENE"[1]

Sir:

The simplest scheme for the biosynthesis of bulnesol[2] (I) from farnesyl pyrophosphate requires only two reactions, each involving formation of a ring. Because of the simplicity of this scheme and the ease with which bulnesol may be converted (on paper) by carbonium ion type reactions into patchouli alcohol[3] (II), guaiol[2,4] (III), "δ-guaiene"[5]



(1) Terpenoids. III.

(2) H. Minato, *Tetrahedron Letters*, **8**, 280 (1961); F. Šorm, L. Dolejš and A. Mironov, *Coll. Czech. Chem. Comm.*, **26**, 1015 (1961).

(3) G. Büchi, R. E. Eriksen and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961).