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# RESEARCH ON PYRAZOLES. XLVII.* SYNTHESIS OF PYRAZOLES WITH LONG-CHAIN ALKYL SUBSTITUENTS

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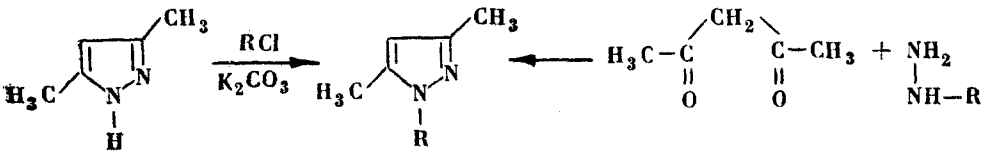
A number of alkylpyrazoles with long alkyl side chains are synthesized.

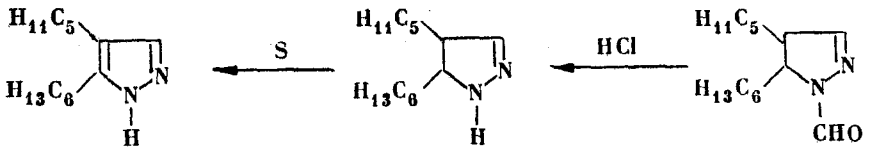
In investigating the pharmacological activity of a number of pyrazole derivatives [2, 3], it was found that alkylpyrazoles have an appreciable effect on the central nervous system. To investigate this effect in greater detail, a number of alkylpyrazoles with long alkyl side chains at positions 1 and 3 were synthesized.

Various N-substituted 3, 5-dimethylpyrazoles could be synthesized most simply, by alkylating 3, 5-dimethylpyrazole. Conditions for alkylation with RCl and potash were found giving yields up to 90% (see Table 4). Condensation of alkylhydrazines with acetylacetone could also be utilized.



The alkylhydrazines ($C_5$—$C_{12}$) for this and subsequent reactions were synthesized by a somewhat modified method [4], which made it possible to avoid using the more expensive alkyl bromides (see Table 1). Pyrazoles with a long alkyl side chain at position 3 were synthesized by the method used in [5] for synthesizing β-chlorovinylketones from acid ($C_6$—$C_8$) chloroanhydrides, with certain modifications. The yields were approximately 80% (see Table 2). On condensation with hydrazone, the resulting β-chlorovinylketones gave 1, 3-disubstituted pyrazoles in 75-85% yields (see Table 3).

4-Amyl-5-hexylpyrazole was prepared from heptanal azine by the method previously described in [6] through a stage involving dehydration of a pyrazoline with acid [7].



Investigation of the physiological effect on the central nervous system of all the pyrazoles with over 10 carbon atoms showed that they were inactive.

## EXPERIMENTAL

Alkylhydrazines. 0.4 mole of the alkyl chloride is added dropwise, in 4 hr 30 min, to a refluxing mixture of 150 g (approximately 3 mole) 96% hydrazine hydrate, 500 ml isopropanol (or propanol), and 6 g KI, while stirring very vigorously. Refluxing is continued for 6 hr more, with energetic stirring, until the mixture emulsifies, when the alcohol is distilled off. After all the alcohol (500 ml) has distilled over, 80 ml benzene, then 0.4 mole (16 g) sodium hydroxide is added to the residue, and the mixture is stirred until the alkali has completely dissolved (about 10 min). The lower layer of hydrazine hydrate (120 ml) is separated off and used in the next synthesis, and the upper benzene layer (containing alkyl hydrazine) vacuum-distilled in a current of nitrogen (Table 1).

β-Chlorovinylketones. Acetylene (freed from moisture and acetone) is bubbled into a mixture of 1000 ml $CCl_4$ (dried by shaking with phosphorus pentoxide), 200 g (approximately 1.5 mole) anhydrous aluminum chloride, 1 g mercuric chloride, and 1.5 mole acid chloroanhydride at 10°. The acetylene is bubbled at such a rate that the temperature is held at 9-10° (exothermic reaction, external bath temperature 2-3°). Once further passage of acetylene ceases to cause further evolution of heat, it is passed for another 10 min. The reaction products are poured onto 800 g ice, 15 ml concentrated hydrochloric acid are added, the $CCl_4$ layer is separated off and washed with 400 ml water, the $CCl_4$ distilled off, and the residue vacuum-distilled (Table 2).

*For part XLVI see [1].

Cyclizing β-chlorovinylketones with hydrazines (Table 3). A solution of 1 mole of the hydrazine in 50 ml benzene is added dropwise and slowly to a solution of 1 mole β-chlorovinylketone in 150 ml benzene, which is stirred and cooled (exothermic reaction). Then the whole is stirred for 1 hr at 80°. The products are cooled, stirred, and 1 mole sodium hydroxide in 200 ml water is added slowly. Then, when addition is complete, stirring is continued for 30 min longer. The layers are separated, and the upper layer, benzene, vacuum-distilled.

Alkylation of pyrazoles (Table 1, 4). A mixture of 1 mole pyrazole, 1 mole alkyl halide, and 0.52 g mole anhydrous potash, slightly sprinkled with water, is refluxed, with good stirring, at 200° for five hours. The reaction products are washed with 2N bicarbonate solution, then with water, and vacuum-distilled.

Heptanal (enanthal) azine. 57 ml 100% hydrazine hydrate are slowly dropped into a well-stirred and externally cooled (running water) mixture of 251 g freshly distilled heptanal (bp 72-76° (65 mm). Stirring is continued for 1 hr after addition is complete, then the product is filtered, and the lower layer removed. The upper one is dried by stirring for one hour with 20 g anhydrous magnesium sulfate, which is then filtered off and the filtrate vacuum-distilled. Yield 194 g azine (79%), bp 176-180° (24 mm), 151-155° (13 mm), $n_D^{20}$ 1.4590, $d_4^{20}$ 0.8349. Uv spectrum $\lambda_{max}$ 220 mμ, log ε 3.62 (SF-4 spectrophotometer, solvent methanol). Found: N 12.17, 12.13%. Calculated for $C_{14}H_{28}N_2$: N 12.48%.

1-Formyl-4-amyl-5-hexylpyrazoline. 448 g heptanal azine are added with vigorous stirring to 138 g dry formic acid at such a rate that the temperature does not rise above 50°. When the dropwise addition is finished, the mixture is left for six hours, and then kept at 80°. The total products are then vacuum-distilled, to give 395 g (78%) of the formyl derivative, bp 196-198° (7 mm), $n_D^{20}$ 1.4775, $d_4^{20}$ 0.9271. Uv spectrum $\lambda_{max}$ 223 mμ, log ε 3.38. Found: N 10.97, 10.79%. Calculated for $C_{15}H_{28}N_2O$: N 11.09%.

4-Amyl-5-hexylpyrazoline. A mixture of 29 g of the formyl derivative and 120 ml hydrochloric acid (1:2) is refluxed for four hours, the aqueous layer rejected, and the oily one washed with 2N sodium bicarbonate solution, then with water, and vacuum-distilled in a stream of inert gas, to give 19 g (83%) of pyrazoline, bp 186-201° (21 mm); $n_D^{20}$ 1.4680, $d_4^{20}$ 0.8842. Uv spectrum $\lambda_{max}$ 220 mμ, log ε 3.11. Found: N 11.97, 11.91%. Calculated for $C_{14}H_{28}N_2$: N 12.48%.

4-Amyl-5-hexylpyrazole. A mixture of 22.4 g pyrazoline and 3.2 g sulfur are heated in a metal bath at 240° until evolution of hydrogen sulfide ceases. Vacuum distillation of the reaction product gives 17 g (76.5%) pyrazole, bp 190-194° (9 mm), $n_D^{20}$ 1.4782, $d_4^{20}$ 0.8994. Uv spectrum $\lambda_{max}$ 226 mμ, log ε 4.11. Found: N 12.64, 12.61%. Calculated for $C_{14}H_{26}N_2$: N 12.58%.

4-Amyl-5-phenylpyrazoline. 404 g amylcinnamic aldehyde in 200 ml isopropanol are added to 250 ml 96% hydrazine hydrate plus 300 ml isopropanol refluxing in a flask at such a rate that the solution boils steadily. After addition is complete boiling is continued for a further three hours, and then the isopropanol, excess hydrazine, and water formed are distilled off under a water pump vacuum. The mass of pyrazoline remaining is used directly for the dehydration, mass 428 g (100%).

4-Amyl-5-phenylpyrazole. 60 g stick sulfur are added, in 10 g portions, to the 428 g of crude pyrazolone obtained in the previous experiment, brought to 190°, and the mixture heated at 190-200° until hydrogen sulfide evolution ceases (about 3 hr). Then the total products are vacuum-distilled to give 127 g (30%) of a fraction bp 202-204° (8 mm), $n_D^{20}$ 1.5630, $d_4^{20}$ 1.0392. Found: N 12.86, 12.63%. Calculated for $C_{14}H_{20}N_2$: N 12.93%.

TABLE 1

Alkhydrazines

| Hydrazine | Bp, °C (pressure, mm) | $n_D^{20}$ | $d_4^{20}$ | Formula | N, % | | Yield, % |
|---|---|---|---|---|---|---|---|
| | | | | | Found | Calc. | |
| n-Amyl | 62—64(9) | 1.4432 | 0.8448 | $C_5H_{14}N_2$ | 27.86; 27,80 | 27.41 | 76 |
| n-Heptyl | 103—105(21) | 1.4448 | 0.8377 | $C_7H_{18}N_2$ | 21.79; 21,63 | 21.48 | 82 |
| n-Octyl | 112—118(18) | 1.4452 | 0.8383 | $C_8H_{20}N_2$ | 19.78; 19,67 | 19.44 | 83 |
| n-Nonyl | 110—114(11) | 1.4431 | 0.8320 | $C_9H_{22}N_2$ | 18.11; 18,03 | 17.68 | 81 |
| n-Dodecyl | 128—136(2) | 1.4411 | 0.8307 | $C_{12}H_{28}N_2$ | 13.83; 13,70 | 13.98 | 79 |

TABLE 2

β-Chlorovinylketones

| RCOCH=CHCl, where R is | Bp, °C (pressure, mm) | $n_D^{20}$ | $d_4^{20}$ | Formula | Cl, % | | Yield, % |
|---|---|---|---|---|---|---|---|
| | | | | | Found | Calc. | |
| $C_6H_{13}$ | 98(7) | 1.4644 | 0.9852 | $C_9H_{15}ClO$ | 20.46; 20.41 | 20.28 | 80 |
| $C_5H_{11}$ | 122—126(21) | 1.4640 | 0.9927 | $C_8H_{13}ClO$ | 22.34; 22,18 | 22.08 | 79 |

TABLE 3

Substituted pyrazoles

| Pyrazole | Bp, °C (pressure, mm) | $n_D^{20}$ | $d_4^{20}$ | Formula | N, % Found | N, % Calc. | Yield, % |
|---|---|---|---|---|---|---|---|
| 3-(5)-Hexyl | 150°(10) | 1.4188 | 0.9252 | $C_9H_{16}N_2$ | 18.56; 18.47 | 18.37 | 82 |
| 1-Heptyl-3-hexyl | 170(4) | 1.4672 | 0.8823 | $C_{16}H_{30}N_2$ | 11.64; 11.57 | 11.28 | 91 |
| 1, 3-Diamyl | 138(6) | 1.4679 | 0.8939 | $C_{13}H_{24}N_2$ | 13.73; 13.64 | 13.42 | 87 |
| 1-Heptyl-3-amyl | 165(10) | 1.4680 | 0.8821 | $C_{15}H_{28}N_2$ | 12.07; 12.01 | 11.83 | 86 |
| 1-Dodecyl-3-amyl | 205(6) | 1.4685 | 0.8574 | $C_{20}H_{38}N_2$ | 9.37; 9.31 | 9.18 | 77 |
| 1-Octyl-3-amyl | 174(6) | 1.4689 | 0.8779 | $C_{16}H_{30}N_2$ | 11.68; 11.32 | 11.26 | 82 |
| 1-Nonyl-3-amyl | 183(6) | 1.4700 | 0.8802 | $C_{17}H_{32}N_2$ | 10.97; 10.84 | 10.69 | 72 |
| 1-β-phenylethyl-3-amyl | 193(6) | 1.5221 | 0.9643 | $C_{16}H_{22}N_2$ | 11.39; 11.33 | 11.57 | 87 |
| 1-Phenyl-3-amyl | 162(6) | 1.5540 | 0.9796 | $C_{14}H_{18}N_2$ | 13.29; 13.18 | 13.08 | 82 |
| 1-Methyl-3-amyl | 93(6) | 1.4695 | 0.9557 | $C_9H_{16}N_2$ | 18.54; 18.43 | 18.37 | 88 |
| 1-[β-(pyridyl-4')-ethyl]3-amyl | 207(15) | 1.5052 | 0.9677 | $C_{15}H_{21}N_3$ | 17.36; 17.28 | 17.27 | 83 |
| 1-[β-(pyridyl-2')-ethyl]3-amyl | 187(6) | 1.5241 | 1.0084 | $C_{15}H_{21}N_3$ | 17.83; 17.77 | 17.27 | 80 |
| 1-Methyl-3-hexyl | 140(25) | 1.4705 | 0.9112 | $C_{10}H_{18}N_2$ | 16.99; 16.68 | 16.86 | 74 |
| 1-Dodecyl-3-hexyl | 224(7) | 1.4680 | 0.8519 | $C_{21}H_{40}N_2$ | 8.97; 8.88 | 8.72 | 76 |
| 1-Octyl-4-amyl-5-hexyl* | 216(9) | 1.4707 | 0.8810 | $C_{23}H_{44}N_2$ | 8.21; 8.16 | 8.03 | 70 |
| 1-Octyl-4-amyl-5-phenyl* | 250(15) | 1.5227 | 0.9571 | $C_{22}H_{36}N_2$ | 8.47; 8.36 | 8.51 | 78 |
| 1-Heptyl-4-amyl-5-phenyl* | 238(15) | 1.5261 | 0.9837 | $C_{21}H_{34}N_2$ | 9.07; 8.94 | 8.91 | 82 |
| 1-Butyl-4-amyl-5-phenyl* | 204(12) | 1.5350 | 0.9837 | $C_{18}H_{28}N_2$ | 10.34; 10.31 | 10.28 | 81 |
| 1-Isoamyl-4-amyl-5-phenyl* | 220(19) | 1.5367 | 0.9770 | $C_{19}H_{30}N_2$ | 9.84; 9.63 | 9.77 | 80 |

*Actually in all these cases 1, 3, 4-substituted pyrazole is also present [8].

TABLE 4

1-Substituted 3, 5-dimethylpyrazoles

| 1-R-3, 5-Dimethylpyrazole, where R is | Bp, °C (pressure, mm) | Mp, °C | $n_D^{20}$ | $d_4^{20}$ | Formula | N, % Found | N, % Calc. | Mp picrate (from methanol), °C | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| Dodecyl | 180—184 (16) | 22—23 | — | — | $C_{17}H_{32}N_2$ | 10.51; 10.47 | 10.59 | 32 | 84 |
| Octadecyl | 210—215 (2) | 44—45 | | | $C_{21}H_{40}N_2$ | 7.96; 7.83 | 8.04 | 52,5—53 | 83 |
| Cetyl | 215—220 (12) | 36—37 | | | $C_{23}H_{44}N_2$ | 8.93; 8.79 | 8.74 | 46,5—48 | 86 |
| Nonyl | 168—170 (23) | — | 1.4688 | 0.8950 | $C_{14}H_{26}N_2$ | 12.47; 12.41 | 12.60 | 56—57 | 88 |
| Benzyl | 154—156 (18) | — | 1.5472 | 1.0378 | $C_{12}H_{14}N_2$ | 15.27; 15.11 | 15.03 | 129 | 91 |
| β-Phenylethyl | 150—152 (12) | — | 1.5376 | 1.0280 | $C_{13}H_{16}N_2$ | 14.06; 14.00 | 13.98 | 136,5—137 | 86 |
| Octyl | 149—151 (20) | — | 1.4685 | 0.8954 | $C_{13}H_{24}N_2$ | 13.29; 13.14 | 13.45 | 119—120 | 83 |
| Isoamyl | 211—213 (760) | — | 1.4700 | 0.9364 | $C_{10}H_{18}N_2$ | 16.91; 16.91 | 16.85 | 69—70 | 76 |
| Butyl | 203—207 (760) | — | 1.4736 | 0.9391 | $C_9H_{16}N_2$ | 18.53; 18.51 | 18.41 | — | 77 |
| Heptyl | 137—139 (20) | — | 1.4678 | 0.9038 | $C_{12}H_{22}N_2$ | 14.34; 14.13 | 14.41 | 73—74 | 81 |
| 2-Ethylhexane | 137(17) | — | 1.4710 | 0.9079 | $C_{13}H_{24}N_2$ | 13.29; 13.16 | 13.45 | 85—86 | 47 |

REFERENCES

1. I. I. Grandberg, KhGS, 279, 1956.
2. G. N. Pershin, N. A. Novitskaya, A. N. Kost, and I. I. Grandberg, DAN, 123, 200, 1953.
3. V. N. Vikhleev, V. N. Il'inskii, K. S. Raevskii, Yu. M. Batulin, I. I. Grandberg, and A. N. Kost, Farmakol. i toksikol., 25, no. 1, 27, 1962.
4. A. N. Kost and R. S. Sagitullin, Author's Certificate, 126117, 1959.
5. A. N. Nesmeyanov, N. K. Kochetkov, and M. N. Rybinskaya, Izv. AN SSSR, OkhN, 395, 1951.
6. A. N. Kost and I. I. Grandberg, ZhOKh, 26, 2319, 1956.
7. I. I. Grandberg and A. N. Kost, ZhOKh, 28, 3071, 1958.
8. I. I. Grandberg and A. N. Kost, ZhOKh, 30, 208, 1960.

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